Distribution of multiple chronic conditions and their impact on the Spanish population

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Grain by grain, a loaf; stone by stone a castle.

Yugoslavian Proverb

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Outline of this thesis

In Chapter 1, there is a brief review of current knowledge of chronic conditions, multimorbidity, vision impairment, quality of life and disability. Chapter 2 is divided into three sections that present the three papers that constitute the thesis methods and results. In paper 1, we present the assessment of multimorbidity patterns in Spain and the results of the association between chronic physical conditions and chronic mental disorders. Paper 2 covers the association between vision impairment and multimorbidity. It also provides evidence with regard to single physical conditions, mental disorders and cognitive function. Paper 3 offers an evaluation of the relationship between chronic conditions (individually or co-occurring) and disability/quality of life. The thesis concludes with a general discussion and summary of the results (Chapters 3 and 4). In Annex 1, a table presents some data related to visual health that were not included in paper 2. In Annex 2, we present those papers that were published during the drafting of this thesis but are not completely related to it.

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CONTENTS

Abstract

English version

Background

Population aging is a worldwide demographic trend caused by the increase in life expectancy and the gradual decline in fertility over recent decades. High-income countries have the highest prevalence of elderly people. Spain, in particular, is one of the countries with the highest proportion of citizens aged 60+, with an expected prevalence of 38% by 2050. The number of people suffering from chronic conditions is clearly related to the aging trends. In developed countries, most deaths and disease burden are related to chronic conditions. Moreover, this population group accounts for 65% of total health expenditure due to the variety of health services needed by these patients.

Although the need for comprehensive management of patients with multiple co-occurring conditions has been highlighted, policies and guidelines are still focused on the management of individual diseases. Thus, a better understanding of multimorbidity is considered fundamental to the development of new preventive and management strategies. In this context, multimorbidity patterns in the population reflect the way chronic conditions appear in the population and need to be better understood as a vital first step in elaborating these strategies.

In the context of population aging, visual impairment has also emerged as a growing concern in public health. Visual problems are associated with an increased risk of falling, progressively limited activity, higher healthcare utilization, lower quality of life and poorer social participation. There is a need for further research into the relationship between visual impairment and chronic physical, mental and cognitive conditions in the elderly.

Under these circumstances, current health care policies should aim to increase life span cost-effectively while maintaining quality of life and functional ability. Although some studies have assessed the impact of single diseases on quality of life and disability, there is still need for deeper understanding of how chronic conditions affect these aspects of health, especially when they co-occur.

Thus, the main objectives of this thesis are:

1. To examine the distribution of chronic conditions and multimorbidity patterns in the Spanish older adult population.
2. To assess the association between individual physical conditions (e.g., diabetes, angina) and the prevalence of mental disorders in the population over 50 years of age.

3. To evaluate the relationship between physical multimorbidity and the prevalence of mental disorders in the Spanish population over 50 years of age.
4. To study the individual and cumulative impact of chronic physical conditions on visual impairment in the population over 50 years old.
5. To analyze the relationship between visual impairment and the presence of mental disorders and cognitive impairment in the population over 50 years old.
6. To explore the individual and cumulative impact of chronic physical and mental conditions on quality of life and disability in the population over 50 years of age.
7. To examine general trends in quality of life and disability across gender in relation to the individual and cumulative effects of chronic conditions.

Methods

Data from this cross-sectional study were collected from the Collaborative Research on Ageing in Europe (COURAGE) project. A total of 4,583 participants from Spain were included; 3,625 aged over 50. Diagnosis of chronic medical conditions included self-reported medical diagnosis and symptom algorithms (angina, arthritis, asthma, cataracts, chronic obstructive pulmonary disease [COPD], and stroke). Diabetes, edentulism and hypertension had no symptom algorithms since they are considered asymptomatic conditions. Depression and anxiety, according to DSM-IV criteria, were assessed using CIDI algorithms. Visual assessment included objective distance/near visual acuity and subjective visual performance. For the assessment of functioning and disability, the 12-item, validated version of the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) was used. Quality of life was assessed through a modified version of the World Health Organization Quality of Life instrument (WHOQOL) called WHOQOL-AGE that has been specially adapted for the elderly population.

An exploratory factor analysis was conducted to detect multimorbidity patterns in the population over 50 years of age. Crude and adjusted binary logistic regressions were performed to identify the associations between physical and mental conditions. Adjusted models included age, gender, educational level, marital status, urbanicity, and number of physical conditions.

Crude and adjusted binary logistic regressions were conducted to assess the associations between visual impairment and chronic physical conditions, physical multimorbidity, mental

disorders and cognitive impairment. Covariates included gender, age, education level, marital status, urbanicity, and employment status.

Crude and adjusted multiple linear regressions were performed to detect associations between chronic conditions and quality of life, and between chronic conditions and disability. The model was adjusted for age, gender, educational level, marital status, urbanicity, all chronic conditions and those interactions with $p<0.2$. Separate models were used to assess the importance of the increasing number of diseases on quality of life and disability, adjusting for same covariates. Additional analogous regressions were performed for males and females to assess gender trends.

Results

Multimorbidity occurred in 20% of the overall Spanish adult population. The prevalence of multimorbidity increased with age from 4% in males between 18 and 49 years (group with the lowest prevalence) up to 67.3% in women over 65 years (group with the highest prevalence). Prevalence of all chronic conditions, except for anxiety, was higher in the population over 65. Women had higher rates of multimorbidity, although only depression, cataracts and arthritis showed higher rates than men when assessed individually.

Three multimorbidity patterns emerged: 'cardio-respiratory' (angina, asthma, chronic lung disease), 'mental-arthritis' (arthritis, depression, anxiety) and the 'aggregated pattern' (angina, hypertension, stroke, diabetes, cataracts, edentulism, and arthritis). All conditions were related to at least one pattern. The adequacy of the sample was considered acceptable, with a Kaiser-Meyer-Olkin value of 0.7. After adjusting for covariates, angina, arthritis, asthma, chronic lung disease and the number of physical conditions were associated with depression [OR 2.01 (1.40,2.90); OR 1.62 (1.19,2.21); OR 1.86 (1.31,2.64); OR 2.66 (1.84,3.86); OR for 3+ diseases 4.38 (2.31,8.33)]. Angina and the number of physical conditions were associated with a higher risk of anxiety [OR 3.39 (1.84,6.22); OR for 3+ diseases 5.23 (1.76,15.53)].

The number of chronic physical conditions was found to be associated with poorer results in both distance and near visual acuity [OR for 3+ diseases 1.75 (1.38,2.23); OR for 3+ diseases 1.69 (1.27,2.24)]. Arthritis, stroke and diabetes were associated with poorer distance visual acuity results after adjusting for covariates [OR 1.79 (1.46,2.21); OR 1.59 (1.05,2.42); OR 1.27 (1.01,1.60)]. Only stroke was associated with near visual impairment [OR 3.01 (1.86,4.87)].

With regard to mental health, poor subjective distance and near visual performance was associated with depression [OR 1.61 (1.14,2.27); OR 1.48 (1.03,2.13)]. Both objective and subjective poor distance and near visual acuity were associated with worse cognitive functioning.

All chronic conditions except hypertension were statistically associated with poor results in quality of life and disability. Depression, stroke and anxiety were found to have the greatest impact on disability [β 15.70 (13.62,17.77); β 12.15 (8.08,16.22); β 11.17 (2.49,19.86)] and quality of life [β -14.00 (-15.85,-12.14); β -8.16 (-11.77,-4.55), β -7.82 (-11.57,-4.08)]. The number of chronic conditions was associated with substantially lower quality of life [β for 4+ diseases: -18.10 (-20.95,-15.25)] and greater disability [β for 4+ diseases: 27.64 (24.99,30.29)]. In general, women suffered from higher rates of multimorbidity and poorer results in quality of life and disability. Effect size across gender resulted in small-moderate values.

Discussion

To the best of our knowledge, this is the first study to assess multimorbidity patterns in the general Spanish population. Three multimorbidity patterns emerged. The first, “cardio-respiratory” highlights the interaction between angina, asthma and COPD. The presence of obstruction, restriction and respiratory symptoms have been found to be related to greater risk of cardiovascular disease, even after adjusting for other conditions. Common risk factors, inflammatory states, oxidative stress and atherosclerotic processes may be involved in this association. The second pattern, “mental/arthritis”, included depression, anxiety and arthritis. The underlying mechanism of this relationship is unclear, although it seems probable that arthritis would predict the onset of psychiatric disorders. Additionally, inflammatory issues may also be involved. The third pattern, named, for convenience, the “aggregate pattern”, is a broader one including seven physical conditions: hypertension, diabetes, cataract, stroke, edentulism, angina and arthritis. Complex underlying causes may be involved, such as common risk factors, the metabolic syndrome or inflammatory pathways.

Arthritis, angina and COPD were shown to be associated with a higher prevalence of depression. These physical disorders share unpleasant symptoms (i.e., joint pain, chest pain or shortness of breath) and may be linked to greater disability, isolation and frustration. Only angina showed a statistically significant association with anxiety. Increasing risk of depression and anxiety were found as the number of co-occurring conditions increased. Therefore, our results indicate that certain patients at higher risk of developing mental

disorders could be identified and adequate prevention and management measures implemented.

To date, this is the first study to analyze the association between suffering from co-occurring physical conditions and the risk of visual impairment; highlighting the additive effect of chronic conditions. We found a clear relationship between suffering from various co-occurring chronic physical conditions and poorer distance and near visual performance. The underlying mechanism in this relationship is unknown. By analogy with frailty, in which accumulation of deficits increases vulnerability to adverse outcomes, the co-occurrence of diseases could be related to higher risk of visual impairment. Individually, arthritis, diabetes and stroke also showed associations with poor visual outcomes, underlining the strong associations with these conditions.

With regard to mental health, poor subjective visual acuity was associated with depression. According to the literature, there is controversy on this association in older adults. Our results highlight the importance of this association and the impact of self-perceived impairment on depression. Visual loss may lead to disability and isolation, which would be related to the onset of depression. However, directionality of the causal relationship is not completely clear. No association was found with anxiety, which supports the findings of a limited number of previous studies.

Both objective and subjective poor visual acuity were found to be associated with worse cognitive performance. These results are welcome as there is only limited evidence on this association. Subjective visual impairment resulted in a stronger association, which should be considered in future studies as they are normally based on objective tests. Common physiological pathways and deprivation of sensory input may be involved in this relationship. Further exploration of this association would lead to common measures for these patients, which is especially important since their co-occurrence is related to higher risk of disability.

Our study also shows that most chronic conditions are associated with higher rates of disability and worse quality-of-life outcomes. In fact, all chronic conditions except hypertension were found to be related to poorer outcomes. Moreover, other mainly asymptomatic conditions (diabetes, edentulism) showed only a mild association compared with other conditions, which indicates that symptoms are closely related to disease burden in terms of disability and quality of life. Our results also draw attention to mental disorders since depression and anxiety (together with stroke) were the leading causes of disability and lower quality of life. This last result is especially relevant since most studies tend to obviate

mental health when assessing chronic conditions, and indicates a need to augment levels of care for these patients with regard to disability and quality of life.

The association between the increasing number of chronic conditions and poor outcomes in disability and quality of life was particularly strong. Consequently, multimorbidity patients would benefit from special attention. This subgroup should be identified as a high-risk population requiring preventive, curative or palliative strategies. Our study is the first nationally-representative study in the older Spanish adults assessing the relationship between chronic conditions, and disability and quality of life. Moreover, it contributes to international evidence on this topic through a sound methodology that allows comparison.

Finally, our results show that women had a higher level of disability and poorer quality of life than men. The clinical relevance of this is unclear as there are no clinical cut-offs available for these screening tools and the effect size analysis resulted in small-moderate values. It is noteworthy that, although trends were similar across gender, anxiety and angina were statistically associated with poorer results in women only, while edentulism and asthma were related to poorer results solely in men. Similar trends were found with regard to the impact of the increasing number of co-occurring conditions on quality of life and disability.

Conclusions

1. Multimorbidity is present in a large proportion of the older Spanish population, especially in those aged over 50. The prevalence of multimorbidity affects more than half of men and over two-thirds of women over 65 years. Chronic conditions tend to appear in certain multimorbidity patterns: “cardio-respiratory” (angina, asthma, COPD), “mental arthritis” (arthritis, anxiety, depression), “aggregate pattern” (angina, cataract, hypertension, edentulism, diabetes, arthritis, stroke).
2. With regard to the analysis of the impact of individual physical diseases on mental health, a higher risk of depression is present in people with asthma, angina, COPD and arthritis, whereas only angina is associated with anxiety.
3. The number of chronic conditions is greatly associated with the diagnosis of depression and anxiety.
4. Visual impairment is common in the Spanish older population. Stroke, arthritis and diabetes are individually associated with worse distance visual acuity, while stroke is associated with worse near visual acuity. The number of physical conditions is greatly associated with worse distance and near visual acuity.

5. Subjective distance visual acuity problems are related to a higher risk of depression, while no measure of visual acuity is associated with changes in the prevalence of anxiety. All measures of visual impairment (distance/near and objective/subjective) are related to impaired cognitive functioning.
6. All chronic conditions assessed (angina, anxiety, arthritis, asthma, cataract, COPD, depression, diabetes, edentulism, stroke), except for hypertension, impact negatively on disability and quality of life in the Spanish older population. Stroke and mental disorders (depression, anxiety) are the conditions that have the strongest impact on these outcomes. Conditions with fewer symptoms (diabetes, edentulism, cataract) tend to have a lower impact on health outcomes than those with more symptoms (angina, COPD, arthritis). The number of chronic conditions impacts greatly both on quality of life and disability.
7. Women have slightly poorer results in quality of life and disability than men. Individually, some conditions affect quality of life and disability only in men or women. The effect of the number of chronic conditions is important in both sexes.

Abstract

Spanish version

Introducción

El envejecimiento de la población es una tendencia demográfica global causada por el incremento de la esperanza de vida y la disminución de la tasa de fertilidad en las últimas décadas. Los países desarrollados sufren altos índices de envejecimiento, siendo España uno de los países con mayor prevalencia de población mayor de 60 años. En este sentido, se estima que este grupo de población supondrá el 38% del total en 2050. A su vez, el envejecimiento de la población se asocia intensamente con la prevalencia de condiciones crónicas. Estas circunstancias se relacionan con un elevado uso de servicios sanitarios de la población mayor, que comporta el 65% del gasto sanitario.

Aunque en los últimos años se ha destacado la necesidad de un manejo integral de los pacientes con condiciones múltiples, las políticas sanitarias y las guías clínicas todavía centran su atención en las diferentes condiciones de forma individual. Por eso, un mejor entendimiento de la multimorbilidad se considera uno de los pilares para proporcionar nuevas estrategias de prevención y gestión de pacientes. En este contexto, los patrones de multimorbilidad reflejan la forma en que las enfermedades crónicas aparecen en la población, y deberían ser identificados y entendidos como un primer paso para avanzar en este campo.

Por otra parte, en el contexto actual de envejecimiento de la población, los problemas visuales suponen una preocupación creciente a nivel de salud pública. Estos problemas se asocian a un riesgo aumentado de caídas, movilidad limitada, elevado uso de servicios, peor calidad de vida y menor participación social. Es necesaria más investigación en torno a la asociación entre los problemas visuales y las enfermedades crónicas en la gente mayor, incluyendo las condiciones físicas, los problemas mentales y la función cognitiva.

Bajo estos condicionantes las políticas sanitarias deben priorizar el aumento de la esperanza de vida junto al mantenimiento de la calidad de vida y la capacidad funcional de la población. Aunque algunos estudios han evaluado el impacto individual de las condiciones crónicas sobre la calidad de vida y la discapacidad, es necesario investigar de forma más exhaustiva como afectan estas condiciones en estos aspectos de la salud, especialmente cuando ocurren de forma simultánea.

Los objetivos de esta tesis son:

1. Examinar la distribución de las condiciones crónicas y los patrones de multimorbilidad en la población adulta mayor española.

2. Determinar la asociación entre las condiciones físicas (ej.: diabetes, angina) y la prevalencia de problemas mentales en la población española mayor de 50 años.
3. Evaluar la relación entre la multimorbilidad física con la prevalencia de problemas mentales en la población española mayor de 50 años.
4. Estudiar el efecto individual y cumulativo de las enfermedades físicas crónicas sobre la función visual en la población mayor de 50 años.
5. Analizar la relación entre la discapacidad visual y la presencia de problemas mentales y deterioro cognitivo en la población mayor de 50 años.
6. Explorar el impacto individual y cumulativo de las condiciones crónicas físicas y mentales sobre la calidad de vida y la discapacidad de la población mayor de 50 años.
7. Examinar las tendencias generales de calidad de vida y discapacidad por género en relación al efecto individual y cumulativo de las condiciones crónicas.

Métodos

Los datos de este estudio transversal provienen del estudio "Collaborative Research on Ageing in Europe" (COURAGE). Se incluyeron un total de 4,583 participantes de España, 3,625 por encima de los 50 años de edad. El diagnóstico de condiciones crónicas médicas consistió en el diagnóstico médico informado por el paciente y algoritmos sintomáticos (angina, artritis, asma, cataratas, enfermedad pulmonar obstructiva crónica [EPOC], e ictus). No se incluyeron algoritmos sintomáticos para diabetes, edentulismo e hipertensión al considerarse condiciones principalmente asintomáticas. La evaluación de depresión y ansiedad se realizó mediante algoritmos del World Health Organization Composite International Diagnostic Interview (CIDI questionnaire), de acuerdo con criterios Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). La evaluación visual incluyó test de agudeza visual para visión de lejos y de cerca, así como evaluación subjetiva de la visión. Para la evaluación de la discapacidad se utilizó una versión validada de 12 ítems del World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0). La calidad de vida se evaluó mediante una versión modificada del World Health Organization Quality of Life instrument (WHOQOL), llamada WHOQOL-AGE, que ha sido especialmente preparada y validada para la población mayor.

Se utilizó la técnica de factor de análisis exploratorio para detectar patrones de multimorbilidad en la población mayor de 50 años. Se realizaron regresiones logísticas crudas y ajustadas para identificar las asociaciones entre patologías físicas y mentales. Los modelos

ajustados incluyeron: edad, género, nivel educativo, estado civil, patrón urbano, y número de condiciones físicas.

Se efectuaron regresiones logísticas crudas y ajustadas para valorar la asociación entre el déficit visual y las condiciones físicas, la multimorbilidad física, los problemas mentales y la función cognitiva. Las covariables incluyeron: edad, sexo, nivel educativo, estado civil, patrón urbano, y situación laboral.

Finalmente, se realizaron regresiones lineares múltiples para detectar las asociaciones establecidas entre las condiciones crónicas y la calidad de vida, así como de entre las condiciones crónicas y la discapacidad. El modelo se ajustó por edad, género, nivel educativo, estado civil, el resto de condiciones y aquellas interacciones con $p<0.2$. Se realizaron modelos separados para evaluar la importancia del número de condiciones respecto a las mismas variables, ajustando por las mismas covariables. De forma análoga, se realizaron estos mismos análisis para hombres y mujeres con el objetivo de evaluar las tendencias por género.

Resultados

Se observó una prevalencia de multimorbilidad del 20% en la población adulta española. Esta aumentó con la edad desde el 4.0% en hombres de entre 18 y 49 años (grupo con la menor prevalencia) hasta el 67.3% en mujeres mayores de 65 años (grupo con la mayor prevalencia). La prevalencia fue superior para todas las condiciones en el grupo de edad mayor de 65 años, excepto para ansiedad. La proporción de mujeres que sufrían multimorbilidad fue superior que la de los hombres, aunque al comparar la prevalencia de condiciones individualmente sólo se observaron diferencias respecto a depresión, cataratas y artritis.

Se detectaron tres patrones de multimorbilidad: “cardio-respiratorio” (angina, asma, EPOC), “mental-artritis” (artritis, depresión, ansiedad) y el “patrón agregado” (angina, hipertensión, ictus, diabetes, cataratas, edentulismo y artritis). Todas las condiciones se relacionaron al menos con un patrón. La adecuación de la muestra se consideró aceptable, con un valor en el test de Kaiser-Meyer-Olkin de 0.70. Angina, artritis, asma, EPOC y el número de condiciones físicas se asociaron con depresión después de ajustar por covariables [OR 2.01 (1.40,2.90); OR 1.62 (1.19,2.21); OR 1.86 (1.31,2.64); OR 2.66 (1.84,3.86); OR para 3+ condiciones 4.38 (2.31,8.33)]. Por su parte, la angina y el número de condiciones físicas se asociaron a un mayor riesgo de ansiedad [OR 3.39 (1.84,6.22); OR para 3+ condiciones 5.23 (1.76,15.53)].

El número de condiciones crónicas físicas se asoció con malos resultados de agudeza visual de lejos y de cerca [OR para 3+ condiciones 1.75 (1.38,2.23); OR para 3+ condiciones 1.69 (1.27,2.24)]. Artritis, ictus y diabetes se asociaron a malos resultados de agudeza visual de lejos [OR 1.79 (1.46,2.21); OR 1.59 (1.05,2.42); OR 1.27 (1.01,1.60)]. Solo el ictus se asoció a peores resultados de agudeza visual de cerca [OR 3.01 (1.86,4.87)]. En relación a los problemas mentales, una peor agudeza visual subjetiva de lejos y de cerca se asoció a depresión [OR 1.61 (1.14,2.27); OR 1.48 (1.03,2.13)]. Tanto los problemas visuales a nivel objetivo (agudeza visual), como subjetivos resultaron asociados con peor función cognitiva (tanto para visión de lejos como de cerca).

Todas las condiciones crónicas excepto la hipertensión resultaron asociadas con peores resultados en calidad de vida y discapacidad. Depresión, ictus y ansiedad fueron las condiciones con mayor impacto sobre discapacidad [β 15.70 (13.62,17.77); β 12.15 (8.08,16.22); β 11.17 (2.49,19.86)], y calidad de vida [β -14.00 (-15.85,-12.14); β -8.16 (-11.77,-4.55); β -7.82 (-11.57,-4.08)]. El número de condiciones crónicas se relacionó fuertemente con peores resultados en calidad de vida [β 4+ condiciones: -18.10 (-20.95,-15.25)] y mayor discapacidad [β 4+ condiciones: 27.64 (24.99,30.29)]. En general las mujeres sufrieron mayores tasas de multimorbilidad y peores resultados a nivel de discapacidad y calidad de vida. Se calculó el efecto del tamaño para estas variables entre hombres y mujeres, resultando en valores pequeños-moderados.

Discusión

Según nuestro conocimiento, este es el primer estudio que evalúa los patrones de multimorbilidad en la población general española. Se detectaron tres patrones. En el primero, "cardio-respiratorio", se manifiesta la interacción entre angina, asma y EPOC. La presencia de obstrucción, restricción y otros síntomas respiratorios se ha relacionado anteriormente con mayor riesgo de enfermedad cardiovascular, incluso al ajustar por otras enfermedades. En esta asociación podrían estar involucrados: factores de riesgo compartidos, un estado pro-inflamatorio, el estrés oxidativo y los procesos ateroscleróticos. El segundo patrón, "mental-artritis", incluyó la depresión, la ansiedad y la artritis. El mecanismo subyacente a esta relación es incierto, aunque parece probable que la artritis predeciría el inicio de los problemas mentales. Además, diversos aspectos a nivel inflamatorio podrían estar involucrados. El tercer patrón, artificialmente llamado "patrón agregado", es un patrón más extenso que incluye siete condiciones físicas: hipertensión, diabetes, cataratas, ictus,

edentulismo, angina y artritis. Relaciones complejas podrían estar involucradas en el mismo, como factores de riesgo compartidos, el síndrome metabólico, la vía inflamatoria, etc.

Artritis, angina y EPOC resultaron asociadas a una mayor prevalencia de depresión. Estas tres condiciones conducen a diversos síntomas desagradables para el individuo que las padece (ej: dolor en articulaciones, dolor en el pecho o falta de aliento) y estarían asociadas a mayor discapacidad, aislamiento y frustración. Angina fue la única condición física asociada con mayor probabilidad de sufrir ansiedad. Nuestro estudio remarca la importancia de la multimorbilidad en el contexto de la salud mental. Se observó un fuerte aumento de depresión y ansiedad a medida que aumentaba el número de patologías concomitantes. Por eso, nuestro estudio refuerza la idea que ciertos pacientes en mayor riesgo de padecer problemas mentales podrían ser detectados y, por tanto, ser sujetos de programas de prevención y manejo adecuados a su situación.

Hasta la fecha este es también el primer estudio que ha analizado la asociación entre la presencia de multimorbilidad y los problemas visuales, incluyendo el estudio del efecto cumulativo de las condiciones crónicas. Se ha encontrado una relación clara entre el número de condiciones físicas y malos resultados de agudeza visual tanto de cerca como de lejos. El mecanismo subyacente en esta relación es desconocido. De forma análoga al concepto de fragilidad, en el que la acumulación de déficits incrementa la vulnerabilidad a los resultados adversos, la concomitancia de condiciones físicas estaría relacionada con un mayor riesgo de discapacidad visual. Individualmente, artritis, diabetes e ictus mostraron una asociación estadísticamente significativa con los problemas visuales, lo que subraya la fuerte relación entre estas variables.

En relación a la salud mental, malos resultados en agudeza visual se relacionaron con depresión. Existe controversia respecto a esta asociación en los adultos mayores. Nuestros resultados destacan la importancia de la misma y remarcan el impacto de la discapacidad visual autopercibida. La pérdida de visión conduciría a discapacidad y aislamiento, que se relacionaría con el inicio de la depresión. Sin embargo, la direccionalidad de esta relación no es completamente clara. Por otra parte, no se encontró ninguna relación entre visión y ansiedad, en consonancia con los pocos estudios publicados hasta la fecha.

Tanto los problemas visuales medidos de forma objetiva como mediante reporte subjetivo se relacionaron con peores resultados en la función cognitiva. Nuestros resultados arrojan luz sobre este tema, especialmente en el contexto de la evidencia limitada hasta el momento. La relación fue especialmente intensa en relación a la percepción visual subjetiva. Tanto la

privación de los estímulos sensoriales como la afectación de las vías neuronales comunes podrían estar envueltas en esta relación. Un mayor conocimiento de esta relación podría conducir al diseño de estrategias comunes para estos individuos, siendo especialmente importante al haber un mayor riesgo de discapacidad.

Nuestro estudio también ha demostrado que las condiciones crónicas están asociadas a un mayor riesgo de sufrir discapacidad y peor calidad de vida. En realidad, todas las condiciones crónicas excepto la hipertensión se relacionaron con peores resultados en esas variables de salud. Además, otras condiciones que cursan principalmente de forma asintomática (diabetes, edentulismo) se relacionaron de forma débil con estas variables comparadas con otras patologías. Esto indica que los síntomas están íntimamente relacionados con la carga de las distintas condiciones a nivel de discapacidad y calidad de vida. Nuestros resultados destacan, además, la importancia de las enfermedades mentales, ya que la depresión y la ansiedad (juntamente con el ictus) son las tres condiciones que lideran el impacto sobre calidad de vida y discapacidad. Este resultado es especialmente importante ya que la mayoría de estudios hasta la fecha han obviado la inclusión de patologías mentales y debería servir para incrementar la preocupación y cuidado de estos pacientes en relación a su discapacidad y calidad de vida asociadas.

La asociación entre un mayor número de condiciones crónicas y los malos resultados en discapacidad y calidad de vida resultó particularmente intensa. Por este motivo, los pacientes con multimorbilidad se beneficiarían de una atención especial. Podrían ser identificados como un subgrupo de alto riesgo en los que desarrollar estrategias preventivas, curativas y paliativas. Nuestro estudio es el primer estudio representativo de la población general española que evalúa las relaciones entre enfermedades crónicas, discapacidad y calidad de vida. Además, complementa la evidencia internacional en este tema, mediante el uso de una metodología validada que permitirá la comparación con futuros estudios.

Finalmente, nuestros resultados mostraron un mayor nivel de discapacidad y peor calidad de vida en las mujeres. La relevancia clínica de este resultado no es clara ya que no hay puntos de corte disponibles para las herramientas continuas que evalúan discapacidad y calidad de vida y los resultados de tamaño de efecto resultaron pequeños-moderados. Es destacable que, aunque las tendencias son similares en ambos sexos, la angina y la ansiedad se relacionaron con peores resultados sólo en mujeres mientras que el asma y el edentulismo se asociaron con peores resultados solo en hombres. En relación al efecto sobre la discapacidad y la

calidad de vida causada por el incremento de condiciones concomitantes se encontraron resultados similares en ambos sexos.

Conclusiones

1. La multimorbilidad está presente en gran parte de la población adulta española, especialmente en los mayores de 50 años. La prevalencia de multimorbilidad supera ampliamente la mitad de los hombres mayores de 65 años y alcanza dos tercios de las mujeres de ese grupo de edad. Las condiciones crónicas se presentan en determinados patrones de multimorbilidad: "cardio-respiratorio" (angina, asma, EPOC), "mental-artritis" (artritis, ansiedad, depresión), "patrón agregado" (angina, cataratas, hipertensión, edentulismo, diabetes, artritis, ictus).
2. A nivel individual, angina, artritis, asma y EPOC están asociados a un mayor riesgo de depresión. Solamente angina se relaciona con ansiedad.
3. El número de condiciones crónicas se asocia fuertemente con el diagnóstico de depresión y ansiedad.
4. Los problemas visuales son frecuentes en la población adulta mayor española. Ictus, artritis y diabetes se asocian individualmente con peor agudeza visual de lejos, mientras que el ictus también se relaciona con peor agudeza visual de cerca. El número de condiciones físicas se asocia fuertemente a peores resultados de agudeza visual de lejos y de cerca.
5. Los problemas subjetivos de la visión de lejos se relacionan con un mayor riesgo de depresión, pero no de ansiedad. Los problemas visuales (lejos/cerca y objetivo/subjetivo) se asocian a deterioro cognitivo.
6. Todas las condiciones crónicas evaluadas (angina, ansiedad, artritis, asma, catarata, depresión, diabetes, edentulismo, EPOC, ictus), excepto hipertensión, afectan la discapacidad y la calidad de vida de forma negativa en la población española mayor. El ictus y los problemas mentales (depresión, ansiedad) son las condiciones con el efecto más importante en estos resultados. Las condiciones con menos síntomas (diabetes, edentulismo, catarata) tienden a ejercer una menor influencia sobre estas variables de salud comparado con aquellas con más síntomas (angina, EPOC, artritis). El número de condiciones crónicas afecta de forma intensa a nivel de calidad de vida y discapacidad.
7. Las mujeres tienen resultados moderadamente peores que los hombres a nivel de calidad de vida y discapacidad. Individualmente, algunas condiciones afectan la

calidad de vida o discapacidad sólo a las mujeres o a los hombres. El efecto del número de condiciones crónicas es importante en ambos sexos.

Abstract

Catalan version

Introducció

L'envelliment de la població és una tendència demogràfica global causada per l'increment de l'esperança de vida i la disminució de la taxa de fertilitat durant les últimes dècades. Els països desenvolupats pateixen alts índexs d'envelliment, sent Espanya un dels països amb major prevalença de població més gran de 60 anys. En aquest sentit, s'estima que aquest grup de població suposarà el 38% del total al 2050. Al seu torn, l'envelliment de la població s'associa intensament amb la prevalença de les condicions cròniques. Aquestes circumstàncies es relacionen amb un elevat ús de serveis sanitaris de la població envellida, que comporta el 65% de la despesa sanitària.

Tot i que en els darrers anys s'ha destacat la necessitat d'un maneig integral dels pacients amb condicions múltiples, les polítiques sanitàries i les guies clíniques encara centren la seva atenció sobre les diferents condicions de forma individual. Per això, un millor enteniment de la multimorbilitat es considera un dels pilars per proporcionar noves estratègies de prevenció i gestió dels pacients. En aquest context, els patrons de multimorbilitat reflecteixen la manera en què les malalties cròniques apareixen a la població, i haurien de ser reconeguts com un primer pas per avançar en aquest camp de la medicina.

D'altra banda, en el context actual d'envelliment de la població, els problemes visuals suposen una preocupació creixent a nivell de salut pública. Aquests problemes s'associen a un risc augmentat de caigudes, mobilitat limitada, elevat ús de serveis, pitjor qualitat de vida i menor participació social. Cal més investigació al voltant de l'associació entre els problemes visuals i les malalties cròniques en la gent gran, incloent-hi les condicions físiques, els problemes mentals i la funció cognitiva.

Sota aquests condicionants les polítiques sanitàries han de prioritzar l'increment de l'esperança de vida al costat del manteniment de la qualitat de vida i la capacitat funcional de la població. Encara que alguns estudis han avaluat l'impacte individual de les condicions cròniques sobre la qualitat de vida i la discapacitat, és necessari investigar de manera més exhaustiva com afecten aquestes condicions en aquests aspectes de la salut, especialment quan ocorren de manera simultània.

Els objectius principals d'aquesta tesi són:

1. Examinar la distribució de les condicions cròniques i els patrons de multimorbilitat en la població espanyola adulta i envellida.

2. Determinar l'associació entre les condicions físiques (p.e., diabetis, angina) i la prevalença de problemes mentals en la població espanyola major de 50 anys.
3. Avaluar la relació entre la multimorbilitat física i la prevalença de problemes mentals en la població espanfyola de més de 50 anys.
4. Estudiar l'efecte individual i cumulatiu de les malalties cròniques físiques sobre la discapacitat en la població de més de 50 anys.
5. Analitzar la relació entre la discapacitat visual i la presència de problemes mentals i deteriorament cognitiu en la població major de 50 anys.
6. Explorar l'impacte individual i cumulatiu de les condicions cròniques físiques i mentals sobre la qualitat de vida i la discapacitat de la població major de 50 anys.
7. Examinar les tendències generals de qualitat de vida i discapacitat segons gènere en relació a l'efecte individual i cumulatiu de les condicions cròniques.

Mètodes

Les dades d'aquest estudi transversal provenen de l'estudi "Collaborative Research on Ageing in Europe" (COURAGE). Es van incloure un total de 4,583 participants d'Espanya, 3,625 dels quals amb una edat superior als 50 anys. El diagnòstic de condicions cròniques mèdiques va consistir en el diagnòstic mèdic informat pel pacient i algoritmes simptomàtics (angina, artritis, asma, cataractes, malaltia pulmonar obstructiva crònica [MPOC], i ictus). No es van incloure algoritmes simptomàtics per diabetis, edentulisme i hipertensió en considerar-se condicions principalment asimptomàtiques. L'avaluació de depressió i ansietat es va realitzar mitjançant els algoritmes del World Health Organization Composite International Diagnostic Interview (CIDI questionnaire), d'acord amb criteris del Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). L'avaluació visual va incloure tests d'agudesa visual per visió de lluny i de prop, així com l'avaluació subjectiva de la visió. Per a l'avaluació de la discapacitat es va utilitzar una versió validada de 12 ítems del World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0). La qualitat de vida es va avaluar mitjançant una versió modificada del World Health Organization Quality of Life instrument (WHOQOL), anomenada WHOQOL-AGE, validada i especialment preparada per la població d'edat avançada.

Es va utilitzar la tècnica de factor d'anàlisi exploratori per detectar patrons de multimorbilitat a la població major de 50 anys. Es van realitzar regressions logístiques crues i ajustades per identificar les associacions entre les patologies físiques i mentals. Els models

ajustats van incloure: edat, gènere, nivell educatiu, estat civil, patró urbà, i nombre de condicions físiques.

Es van efectuar diferents regressions logístiques crues i ajustades per valorar l'associació entre el dèficit visual i les condicions físiques, la multimorbilitat física, els problemes mentals i la funció cognitiva. Les covariables van incloure: edat, sexe, nivell educatiu, estat civil, patró urbà, i situació laboral.

Finalment, es van realitzar regressions lineals múltiples per detectar les associacions establertes entre les condicions cròniques i la qualitat de vida, així com d'entre les condicions cròniques i la discapacitat. El model es va ajustar per edat, gènere, nivell educatiu, estat civil, la resta de condicions i aquelles interaccions amb p <0.2. Es van realitzar models separats per avaluar la importància del nombre de condicions respecte a les mateixes variables, ajustant per les mateixes covariables. De forma anàloga, es van realitzar aquests mateixos anàlisis per homes i dones amb l'objectiu d'avaluar les tendències per gènere.

Resultats

Es va observar una prevalença de multimorbiditat del 20% en la població adulta espanyola. Aquesta va augmentar amb l'edat des del 4.0% en homes d'entre 18 i 49 anys (grup amb la menor prevalença) fins al 67.3% en dones majors de 65 anys (grup amb la major prevalença). La prevalença va ser superior per a totes les condicions en el grup d'edat major de 65 anys, excepte per ansietat. La proporció de dones que patien multimorbilitat va ser superior que la dels homes, encara que en comparar la prevalença de condicions individualment només es van observar diferències respecte a depressió, cataractes i artritis.

Es van detectar tres patrons de multimorbilitat: "cardio-respiratori" (angina, asma, MPOC), "mental-artritis" (artritis, depressió, ansietat) i un "patró agregat" (angina, hipertensió, ictus, diabetis, cataractes, edentulisme i artritis). Totes les condicions es van relacionar almenys amb un patró. L'adequació de la mostra es va considerar acceptable, amb un valor en el test de Kaiser-Meyer-Olkin de 0.70. Angina, artritis, asma, MPOC i el nombre de condicions físiques es van associar amb depressió després d'ajustar per covariables [OR 2.01 (1.40,2.90); OR 1.62 (1.19,2.21); OR 1.86 (1.31,2.64); OR 2.66 (1.84,3.86); OR per 3+ condicions 4.38 (2.31,8.33)]. Per la seva banda, l'angina i el nombre de condicions físiques es van associar a un major risc d'ansietat [OR 3.39 (1.84,6.22); OR per 3+ condicions 5.23 (1.76,15.53)].

El nombre de condicions cròniques físiques es va associar amb resultats pobres d'agudesa visual de lluny i de prop [OR per 3+ condicions 1.75 (1.38,2.23); OR per 3+ condicions 1.69 (1.27,2.24)]. Artritis, ictus i diabetis es van associar a pitjors resultats d'agudesa visual de lluny [OR 1.79 (1.46,2.21); OR 1.59 (1.05,2.42); OR 1.27 (1.01,1.60)]. Només l'ictus es va associar a pitjors resultats d'agudesa visual de prop [OR 3.01 (1.86,4.87)]. En relació als problemes mentals, una pitjor agudesa visual subjectiva de lluny i de prop es va associar a depressió [OR 1.61 (1.14,2.27); OR 1.48 (1.03,2.13)]. Tant els problemes visuals a nivell objectiu (agudesa visual), com subjectius van resultar associats amb una pitjor funció cognitiva (tant en visió de prop com en visió de lluny).

Totes les condicions cròniques excepte la hipertensió van resultar associades amb pitjors resultats en qualitat de vida i discapacitat. La depressió, l'ictus i l'ansietat van ser les condicions amb major impacte sobre discapacitat [β 15.70 (13.62,17.77); β 12.15 (8.08,16.22); β 11.17 (2.49,19.86)], i qualitat de vida [β -14.00 (-15.85, -12.14); β -8.16 (-11.77, -4.55); β -7.82 (-11.57, -4.08);]. El nombre de condicions cròniques es va relacionar fortament amb pitjors resultats en qualitat de vida [β 4+ condicions: -18.10 (-20.95, -15.25)] i major discapacitat [β 4+ condicions: 27.64 (24.99,30.29)]. En general les dones van patir taxes superiors de multimorbilitat i pitjors resultats a nivell de discapacitat i qualitat de vida. Es va calcular l'*effect size* per a aquestes variables entre homes i dones, resultant en valors petits-moderats.

Discussió

Segons el nostre coneixement, aquest és el primer estudi que avalua els patrons de multimorbilitat en la població general espanyola. Es van detectar tres patrons. Al primer, "cardio-respiratori", es manifesta la interacció entre angina, asma i MPOC. La presència d'obstrucció, restricció i altres símptomes respiratoris s'ha relacionat anteriorment amb major risc de malaltia cardiovascular, fins i tot en ajustar per altres malalties. En aquesta associació podrien estar involucrats: factors de risc compartits, un estat pro-inflamatori, l'estrès oxidatiu i els processos ateroscleròtics. El segon patró, "mental-artritis", va incloure la depressió, l'ansietat i l'artritis. El mecanisme subjacent a aquesta relació és incert, encara que sembla probable que l'artritis prediria l'inici dels problemes mentals. A més, diversos aspectes a nivell inflamatori podrien estar involucrats. El tercer patró, artificialment anomenat "patró agregat", és un patró més extens que inclou set condicions físiques: hipertensió, diabetis, cataractes, ictus, edentulisme, angina i artritis. Diverses relacions

complexes estarien involucrades en el mateix, com a factors de risc compartits, la síndrome metabòlica, la via inflamatòria, etc.

L'Artritis, l'angina i la MPOC van resultar associades a una major prevalença de depressió. Aquestes tres condicions condueixen a diversos símptomes desagradables per a l'individu que les pateix (ex: dolor en articulacions, dolor al pit o manca d'alè) i estarien associades a major discapacitat, aïllament i frustració. L'Angina va ser l'única condició física associada amb major probabilitat de patir ansietat. El nostre estudi remarca la importància de la multimorbilitat en el context de la salut mental. Es va observar un fort augment de patir depressió i ansietat a mesura que augmentava el nombre de patologies concomitants. Per això, el nostre estudi reforça la idea que certs pacients amb major risc de patir problemes mentals poden ser detectats i, per tant, ser subjectes a programes de prevenció i maneig adequats a la seva situació.

Fins ara aquest és també el primer estudi que ha analitzat l'associació entre la presència de multimorbilitat i els problemes visuals, incloent l'estudi de l'efecte acumulatiu de les condicions cròniques. S'ha trobat una relació clara entre el nombre de condicions físiques i pobres resultats d'agudesa visual tant de prop com de lluny. El mecanisme subjacent en aquesta relació és desconegut. De forma anàloga al concepte de fragilitat, en el qual l'acumulació de dèficits incrementa la vulnerabilitat i els resultats adversos, la concomitància de condicions físiques estaria relacionat amb un major risc de discapacitat visual. Individualment, artritis, diabetis i ictus van mostrar una associació estadísticament significativa amb els problemes visuals, el que subratlla la forta relació entre aquestes variables.

En relació a la salut mental, resultats dolents en agudesa visual es van relacionar amb depressió. Existeix controvèrsia respecte a aquesta associació en els adults grans. Els nostres resultats destaquen la importància de la mateixa i remarquen l'impacte de la discapacitat visual autopercebuda. La pèrdua de visió conduiria a discapacitat i aïllament, que es relacionaria amb l'inici de la depressió. No obstant això, la direccionalitat d'aquesta relació no és clara. D'altra banda, no es va trobar cap relació entre visió i ansietat, en concordança amb els pocs estudis publicats fins a la data.

Tant els problemes visuals mesurats de forma objectiva com mitjançant informe subjectiu es van relacionar amb pitjors resultats en la funció cognitiva. Els nostres resultats afavoreixen un major enteniment d'aquesta relació, especialment en el context de la poca evidència disponible fins l'actualitat. Tant la privació dels estímuls sensorials com l'afectació de les vies

neuronals comunes podrien estar implicades en aquesta relació. Un major coneixement d'aquesta relació podria conduir al disseny d'estratègies comunes per a aquests individus, especialment important a l'haver un major risc de discapacitat.

El nostre estudi també ha demostrat que les condicions cròniques estan associades a un major risc de patir discapacitat i pitjor qualitat de vida. En realitat, totes les condicions cròniques excepte la hipertensió es van relacionar amb pitjors resultats en aquestes variables de salut. A més, altres condicions que cursen principalment de forma asimptomàtica (diabetis, edentulisme) es van relacionar de forma feble amb aquestes variables comparades amb altres patologies. Això indica que els símptomes estan íntimament relacionats amb la càrrega de les diferents condicions a nivell de discapacitat i qualitat de vida. Els nostres resultats destaquen, a més, la importància de les malalties mentals, ja que la depressió i l'ansietat (juntament amb l'ictus) són les tres condicions que lideren l'impacte sobre qualitat de vida i discapacitat. Aquest resultat és especialment important ja que la majoria d'estudis fins ara han obviat la inclusió de patologies mentals i hauria de servir per incrementar la preocupació i cura d'aquests pacients en relació a la seva discapacitat i qualitat de vida associades.

L'associació entre un major nombre de condicions cròniques i els mals resultats en discapacitat i qualitat de vida va resultar particularment intensa. Per aquest motiu, els pacients amb multimorbiditat es beneficiarien d'una atenció especial. Podrien ser identificats com un subgrup d'alt risc en què desenvolupar estratègies preventives, curatives i pal·liatives. El nostre estudi és el primer estudi representatiu de la població general espanyola que avalua les relacions entre malalties cròniques, discapacitat i qualitat de vida. A més, complementa l'evidència internacional en aquest tema, mitjançant l'ús d'una metodologia validada que permetrà la comparació amb futurs estudis.

Finalment, els nostres resultats van mostrar un major risc de discapacitat i pitjor qualitat de vida en les dones. La rellevància clínica d'aquest resultat no és clara ja que no hi ha punts de tall disponibles per a les eines contínues que avaluen discapacitat i qualitat de vida i els resultats de magnitud de l'efecte resultar petits-moderats. És destacable que, tot i que les tendències són similars en ambdós sexes, l'angina i l'ansietat es van relacionar amb pitjors resultats només en dones mentre que l'asma i l'edentulisme es van associar amb pitjors resultats només en homes. En relació a l'efecte sobre la discapacitat i la qualitat de vida causada per l'increment de condicions concomitants es van trobar resultats similars en ambdós sexes.

Conclusions

1. La multimorbilitat és present en gran part de la població adulta espanyola, especialment en els majors de 50 anys. La prevalença de multimorbiditat supera àmpliament la meitat dels homes majors de 65 anys i arriba als dos terços de les dones d'aquest grup d'edat. Les condicions cròniques es presenten en determinats patrons de multimorbilitat: "cardio-respiratori" (angina, asma, MPOC), "mental-artritis" (artritis, ansietat, depressió), "patró agregat" (angina, cataractes, hipertensió, edentulisme, diabetis, artritis, ictus).
2. A nivell individual, angina, artritis, asma i MPOC estan associats a un major risc de depressió. Només angina es relaciona amb ansietat.
3. El nombre de condicions cròniques s'associa fortament amb el diagnòstic de depressió i ansietat.
4. Els problemes visuals són freqüents en la població espanyola adulta i envellida. L'ictus, l'artritis i la diabetis es van associar individualment amb una pitjor agudesa visual de lluny, mentre que l'ictus també es va associar a pitjor una agudesa visual de prop. El nombre de condicions físiques s'associa fortament a pitjors resultats d'agudesa visual de lluny i de prop.
5. Els problemes subjectius de la visió de lluny es relacionen amb un major risc de depressió, però no d'ansietat. Tots els problemes visuals (lluny/prop i objectiu/subjectiu) s'associen a deteriorament cognitiu.
6. Totes les condicions cròniques avaluades (angina, ansietat, artritis, asma, cataracta, depressió, diabetis, edentulisme, ictus, MPOC), excepte hipertensió, afecten la discapacitat i la qualitat de vida de manera negativa en la població espanyola. L'ictus i els problemes mentals (depressió, ansietat) són les condicions amb l'efecte més important en aquests resultats. Les condicions amb menys símptomes (diabetis, edentulisme, cataractes) tendeixen a exercir una menor influència sobre aquestes variables de salut comparat amb aquelles amb més símptomes (angina, MPOC, artritis). El nombre de condicions cròniques afecta intensament, de manera negativa la qualitat de vida i la discapacitat.
7. Les dones tenen resultats moderadament pitjors que els homes a nivell de qualitat de vida i discapacitat. Individualment, algunes condicions afecten la qualitat de vida o discapacitat només a les dones o als homes. L'efecte del nombre de condicions cròniques és important en ambdós dos sexes.

Chapter 1
Introduction

1.1. Population aging and chronic conditions

Population aging is taking place in almost all countries, although high-income countries have the highest proportion of elderly people. This process is, in turn, associated with an exponential increase in multimorbidity.

1.1.1. Aging trends

The population aged over 60 years is expected to double between 2000 and 2050, rising from 10% to 20% of the global population [1]. By this time, two billion people will be over 60 years [1]. Regarding the oldest old, those aged over 80 years will have quadrupled by 2050 [1].

This transition is rooted in the increase in life expectancy and the gradual decline in fertility over recent decades. The global fertility rate has fallen from 5 to 2.5 children per woman and life expectancy has increased by 20 years since 1950 [2]. There are, however, great differences among high-, middle-, and low-income countries. In Europe, the elderly population reached 23% of the total population in 2013 due to earlier improvements in living conditions and healthcare systems compared with middle- and low-income countries [3,4]. In fact, Europe is the area with the highest proportion of older people and is projected to continue to be so over coming decades [5]. Other countries such as the USA or Canada have experienced similar aging trends. The increase in prevalence of chronic conditions is recent but fast in low-, and middle-income countries, which must face communicable and chronic diseases simultaneously with scarce resources and limited healthcare systems. Population aging needs to be analyzed taking geographical variations into account.

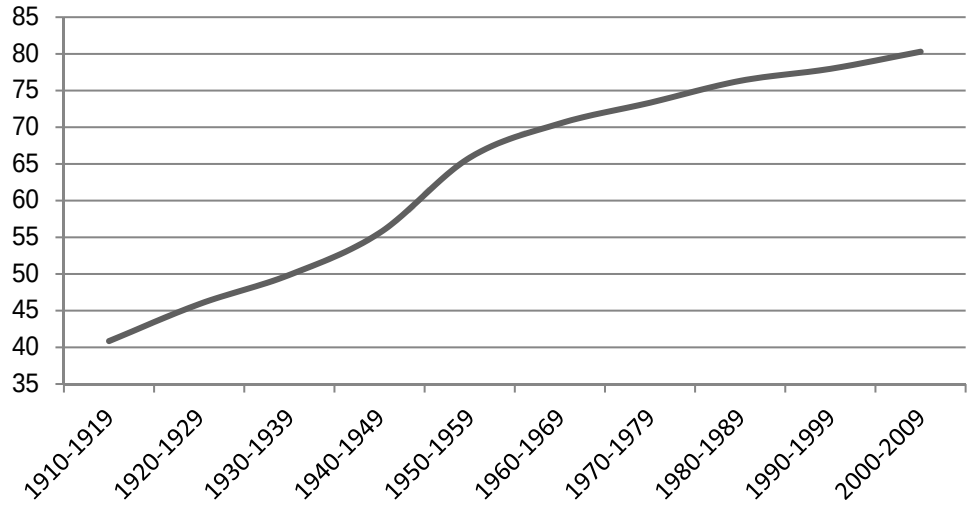

Figure 1. Life expectancy evolution in Spain over the last century. Source: www.mortality.org

In Spain, life expectancy increased enormously in the last 100 years, from 41.2 to 82.1 years [6,7] (Figure 1). Along with this trend, the fertility rate decreased to 1.44 babies per woman in 2013 [8]. In Spain, the aged population accounts for 23% of the total population and is expected to rise to 38 % and reach the 7th position among countries with the highest proportion of citizens over 60 years [2,3] (Figure 2). As in other European Countries, women have a higher life expectancy than men (85.0 years versus 79.2 years) [7].

Population aging and low fertility rates have several implications, such as future population falls. In Spain, relative population growth is expected to diminish and become negative in the next few decades [9]. As this happens, total population is expected to decrease due to the current negative migratory balance, mainly among the working-age population [8]. Thus, income taxes from a lower active population will have to cover the expenses of a social security system faced with the increasing needs of a bigger retired community. This tendency will become even more marked from 2020 on, when baby boomers reach retirement age. At that point, a huge proportion of the national budget will be allocated to retired inhabitants.

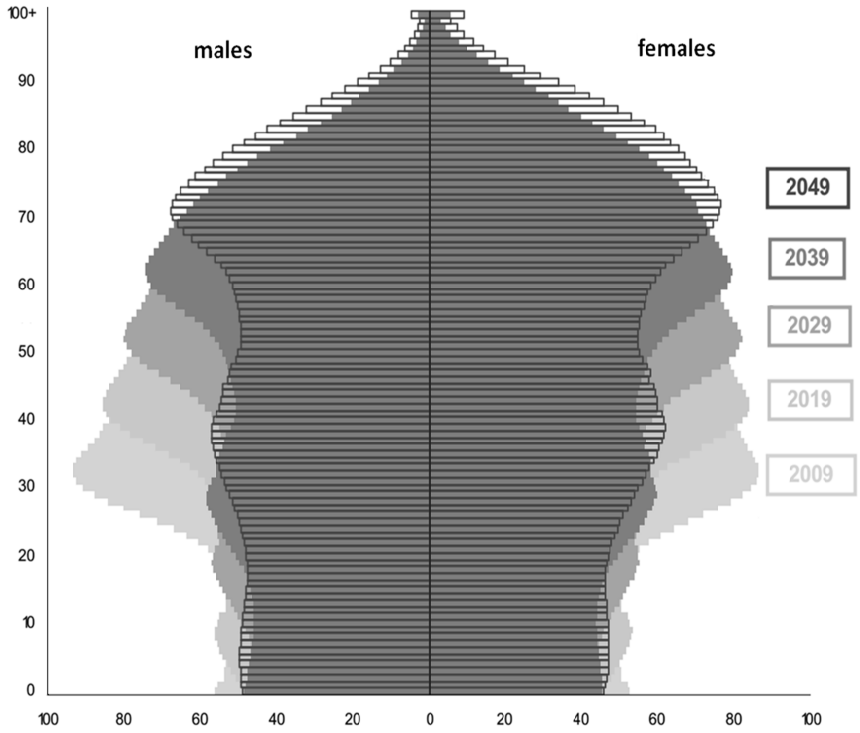

Figure 2. Spanish population pyramid projection. Modified from: Long-Term Projection of the Population of Spain, 2009-2049. 2010. Source: www.ine.es

Recent data have shown that in Spain, as in most European countries, expenditure on social protection and health care amounted to more than 50% of total government expenditure [10]. Moreover, there was a 5% increase in social security expenditure as a percentage of the gross domestic product (GDP) between 2001 and 2011 [10]. This increasing tendency is expected to continue as the population ages. The European Commission has identified population aging as a crucial challenge in the 21st century [11]. Specifically, European Commission has underscored the need to develop an European strategy for chronic conditions [12].

1.1.2. Trends in chronic conditions

The number of people suffering from chronic conditions is increasing and is clearly related to aging trends, which is in turn related to the improvement in living conditions and healthcare [13]. The World Health Organization considers the rise in chronic conditions a worldwide epidemic, accounting for 63% of the 57 million global deaths in 2008 and an estimated projection of 52 million chronic-related deaths by 2030 [14]. In Europe, chronic conditions account for 86% of deaths and 77% of the disease burden [15]. With that regard, over 40% of the population in Europe aged 15 years and over has reported to have a chronic disease [12].

The definition of chronic condition varies widely. Chronic conditions, as showed by Goodman et al, present great heterogeneity with regard to multiple medical characteristics, such as the duration, need for medical attention, causality, and noncontagious nature [16]. There are, however, some shared features. According to the Medical Subject Headings (MeSH), chronic conditions can be defined, in general terms, as those diseases with one or more of the following characteristics: “they are permanent, leave residual disability, are caused by nonreversible pathological alteration, require special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation, or care” [17]. A more simple definition was provided by the World Health Organization: “Chronic diseases are diseases of long duration and generally slow progression” [18].

In order to tackle the increase in chronic conditions, policymakers tend to prioritize those conditions thought to have the greatest impact on the population, measured through quality of life, health care expenditure or life expectancy. The WHO, with a global perspective, proposes prioritizing cardiovascular diseases, cancers, chronic respiratory diseases and diabetes since they are the “world’s biggest killers”, accounting for 80% of all deaths in low- and middle-income countries [19]. These conditions share four behavioral risk factors that can be managed without expensive healthcare measures: physical inactivity, tobacco use,

unhealthy diet and excessive alcohol consumption [19]. At the same time, developed countries can also benefit from these policies.

Over recent decades, high-income countries have seen considerable aging-population trends, so that more specific methodology has been developed and action taken compared with middle- and low-income countries. For instance, the Australian Institute of Health and Welfare include 12 chronic diseases when providing information on chronic conditions: ischaemic heart disease (also known as coronary heart disease), stroke, lung cancer, colorectal cancer, depression, type 2 diabetes, arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and oral disease. In the United States, the Health & Human Services Office of the Assistant Secretary of Health (OASH) drew up the OASH list, containing 20 selected conditions. This list aims to offer a shorter, more useful list of diseases for the study of chronic conditions, compared with older systems that identified up to 185 conditions [16].

In Spain, the National Health Survey shows the high prevalence of chronic conditions in the population, with 42.5% of the population aged 16+ suffering from one or more diseases. This percentage rises to 80.7% in the population over 85 years old [20] (TABLE 1). As found in previous reports, the majority of chronic conditions are more prevalent in the elderly in Spain, with the exception of thyroid problems.

In Spain, more than half of hospital admissions involve the elderly, who also have longer stays [7]. The cost of chronic conditions reaches 65% of total health expenditure, due to the need for a wide variety of health services, such as physician consultation, hospitalization, medication, rehabilitation, long-term care or transportation [21,22]. Moreover, non-communicable conditions have become the leading causes of mortality, and can lead to substantial disability and reduced quality of life. In Spain, the percentage of deaths involving the aged has increased from 30% to 84.1% in the last 100 years [7]. Disability rates for the Spanish population over 65 years reach 30.3%, and rise to 51.5% in the population aged 80 years and older [7]. As would be expected, chronic conditions are responsible for a high proportion of disability. For example, 59% of disability-adjusted life years (DALYs) are associated with chronic conditions [12].

Table 1. Main chronic conditions in Spain. National Health survey (2012). Source: www.ine.es

CHRONIC CONDITION	Population 16+	Population 85+
Arthrosis or arthritis	19.37	62.41
Hypertension	18.73	51.08
Chronic back pain (lumbar)	20.53	31.87
Urinary incontinence	3.77	30.42
Cataracts	5.01	27.8
Chronic back pain (cervical)	17.97	27.6
Varicose veins in the legs	13.56	26.76
Other heart diseases	4.65	23.7
Hypercholesterolemia	16.51	22.31
Diabetes	6.99	18.3
Osteoporosis	4.28	15.19
Chronic constipation	4.48	14.86
Chronic bronchitis, emphysema, COPD	3.85	14.1
Other mental disorders	1.64	12.44
Chronic depression	6.48	12.06
Migraine or frequent headache	10.26	9.79
Chronic anxiety	7.65	9.43
Chronic skin diseases	4.59	7.22
Asthma	4.17	7.1
Hemorrhoids	4.81	6.17
Chronic allergy (excluding allergic asthma)	11.4	5.98
Stroke	0.66	5.3
Malignancies	1.28	3.95
Permanent injuries or damages caused by an accident	3.61	3.9
Myocardial infarction	0.78	3.33
Stomach or duodenal ulcer	2.45	3.03
Thyroid problems	4.48	2.91
Cirrhosis, liver dysfunction	0.75	1.48

1.2. Chronic conditions and multimorbidity

The increase in both chronic condition prevalence and life-expectancy is responsible for the high prevalence of co-occurring chronic conditions in the elderly population.

1.2.1. Comorbidity and Multimorbidity: theoretical framework

The study of chronic conditions has evolved greatly over recent years. Historically, most studies on chronic conditions have focused on the study of individual diseases because of the simplicity of the analysis and the fact that health care delivery is mainly addressed to the management of single diseases. As awareness of the association between chronic conditions increased, so did the number of studies that assessed combinations of diseases. On some occasions, a specific pair of conditions has been studied due to theoretical or clinical-based assumptions on physiological links between these conditions [23,24]. For example, this approach has contributed to better knowledge of the association of pairs of mental disorders [25–27] and the association of pairs of metabolic conditions [24]. The cumulative effect of diseases has been introduced gradually in the study of chronic conditions [28]. Two concepts arise when assessing co-occurring conditions: comorbidity and multimorbidity. (Figure 3).

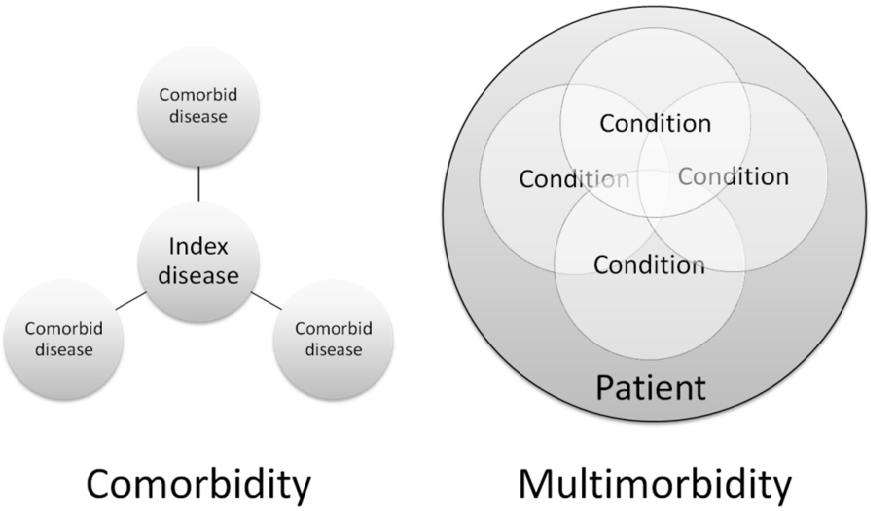

Figure 3. Schematic differences between comorbidity and multimorbidity. Adapted from Boyd CM and Fortin M, 2010.

Comorbidity was defined by Feinstein as “any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study” [29]. This definition depends entirely on the presence of an index or central condition around which the study of other conditions is based. However, this ignores the possible interaction of combinations of diseases that do not include the index disease. Moreover, this framework considers one disease as “central”, which may be unrealistic or unsuitable for

most patient management. The term “comorbidity” has been often adapted or redefined to describe the coexistence of multiple diseases without considering an index disease, which would go beyond exceed its original meaning and overlap with the definition of multimorbidity [30].

Multimorbidity is a relatively new concept in medicine that considers the co-occurrence of diseases in individual patients. In this case, there is not the necessarily one condition which is more “central” than others. The growing interest in the study of multimorbidity is shown in figure 4.

Figure 4. Publications results (title and abstract) on “multimorbidity” in pubmed. Source: http://mltrends.ogic.ca/

There has been, however, a lack of consensus on its definition and different approaches have been considered. Research and clinical definitions can be categorized into three perspectives [31]:

1. **Number of chronic conditions.** This is the most accepted approach in the literature since it reflects the co-occurrence of diseases in a simple and comparable way. There is no agreement on the minimum number of conditions present to classify a patient as “multimorbid”. Although most studies have tended to use 2 or more co-occurring conditions as a cut-off, some others have, arbitrarily, used 3, 4 or more conditions as a minimum threshold for multimorbidity [31]. This approach allows us to assess the direct individual and cumulative effects of chronic conditions at various levels, such as relationship between diseases, the description of multimorbidity patterns and the impact on healthcare outcomes. This definition, unlike the others, only takes the diagnosis of chronic conditions into account.
2. **Number and burden of chronic conditions.** This approach has been found to be especially useful for the assessment of negative health outcomes such as mortality

[32–35] . Examples of these tools are the Charlson Comorbidity index, the Index of Co-Existent Diseases (ICED), the Cumulative Illness Rating Scale (CIRS), The Geriatric Index of Comorbidity (GIC), the Chronic Disease Score, the Kaplan Scale, and The Johns Hopkins Adjusted Clinical Groups (ACG®) system [35]**.** The ACG® system states that the characterization of multimorbidity should include the burden of disease rather than simply the number of diseases [36]. This system classifies all diagnoses into mutually exclusive categories (aggregated diagnosis groups) according to five dimensions: diagnostic certainty, specialty care involvement, etiology, duration and severity of the condition. Risk scores can be computed with the morbidity burden (ACGs) and certain factors (selected medical conditions, hospital dominant conditions, age, gender, pharmacy use and complicated pregnancy marker). Studies taking the broader approach of the Expanded Diagnosis Clusters (EDC) of the ACG® system are comprehensive but complex to conduct outside clinical settings or in cases of poor integration of health care levels [37] . One limitation of these indexes is the need for exhaustive medical records or administrative data and highly trained professionals that have to follow complicated rules in order to compute the indexes [35]. Tooth et al, in one study with 10,434 women, used both unweighted (number of diseases) and weighted (number and burden of diseases) multimorbidity indexes to predict health-related outcomes such as mortality and health and health service use. Although weighted indexes can allow further discrimination between groups, they may lack generalizability to populations other than the specific sample where it was assessed. Tooth et al also found reasonably good results for unweighted scores, with a good linear association between this score and health outcomes. However, the weighted score fitted the data better and the unweighted score led to a more simplistic description due to its narrow range of possible values [38]. The authors stated that in case of simple count of morbidities, selection of diseases must be carefully conducted. Byles et al also stated that the decision regarding selection of the index should be taken in the context of the outcomes to be studied [39]. According to their results, for example, multimorbidity scores incorporating severity may better explain mortality than measures relying on number of diseases.

3. **Combination of chronic conditions with limitations and external factors**. This last definition would be associated with the concept of complexity [31,40]. Le Reste et al conducted a systematic review in which 132 distinct definitions of multimorbidity with 1,631 criteria were found. To address the disparity of multimorbidity definitions, the European General Practice Research Network

presented, in the same paper, a comprehensive definition of multimorbidity: "*Multimorbidity is defined as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor"* [40]. This definition took two or more conditions as the cut-off but the introduction of biopsychosocial and somatic risk factors may be controversial since the article qualifies these issues are qualified as modifiers: "Any biopsychosocial factor, any somatic risk factor, the social network, the burden of diseases, the health care consumption, and the patient's coping strategies may function as modifiers (of the effects of multimorbidity)." The authors admit that it is hard to elucidate whether this definition would be useful at family medicine and nursing care levels, adding that there is need to operationalize biopsychosocial and somatic risk factors [40].

In the context of multiple concurrent diseases or conditions, other common terms have been used besides multimorbidity, such as: pluripathology, multicondition, multipathology, polymorbidity, or polypathology [30]. Diversity in terms and definitions may have a negative impact on practice and research [30]. This disparity makes it necessary to define the terms and criteria used in each study.

1.2.2. Interactions between distinct chronic conditions

There are three main ways to explain the co-occurrence of several conditions in one individual: chance, selection bias or causal associations [41]. By multiplying the prevalence of two conditions in the general population, the prevalence of comorbidity that occurs by chance can be estimated. In multimorbidity research, selection bias refers to clusters (groups of patients with some common characteristics) that are artificially identified or overestimated due to their heavy use of the healthcare system. This bias, also called "Berkson's bias", is widely described in the literature [42]. Chance and selection bias do not represent a real association but have to be taken into account to minimize erroneous assumptions about causality.

Several pathways leading to comorbidity have been described. Valderas et al proposed four main etiological models [41]:

1. **Direct causation**: one condition is totally responsible for the onset of the other; e.g., cataracts caused by diabetes. This model also includes conditions secondary to the medical treatment of the first disease; e.g., cataracts secondary to continued use of glucocorticoids for a certain disease.

2. **Associated factors**: when two diseases are affected by certain risk factors which are also related to each other; e.g., alcohol consumption and smoking with regard to liver disease and lung disease.
3. **Heterogeneity**: in this case several risk factors can have effects on the onset of several diseases; e.g., risk factors (age; smoking) with diseases (cardiovascular diseases, lung cancer).
4. **Independence**: this would be the case of two co-occurring conditions that are caused by a third condition; e.g. cataracts and kidney failure associated with diabetes.

In other cases, a simpler classification has been made, according to overall pathophysiologic risk profile and related management plan, into concordant or discordant associations. An example of concordant association would be diabetes and hypertension while an example of discordant association would be diabetes and prostate cancer [43].

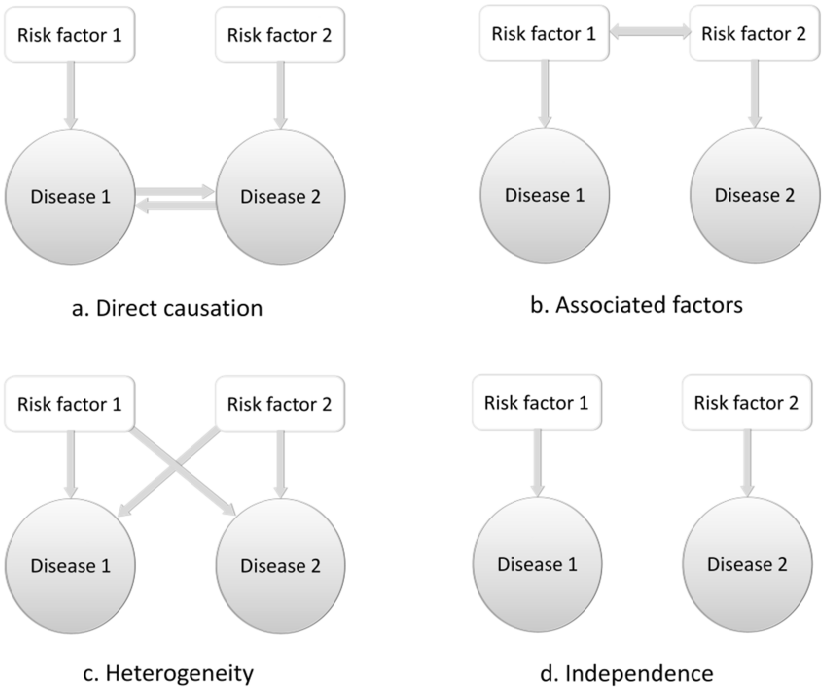

Figure 5. Possible associations between chronic conditions. Adapted from Valderas *et al* [41].

1.2.3. Patterns of multimorbidity

In clinical practice, elderly patients tend to suffer from several co-occurring conditions although there is lack of guidelines considering several conditions simultaneously. Moreover, in research, multimorbidity has mainly been considered as a mere explanatory variable used to adjust for outcomes when performing analyses [44]. A systematic review on

multimorbidity by Marengoni et al concluded that recommendations regarding multimorbidity should be based on a complete and realistic approach, implying need for a better description and understanding of multimorbidity [31]. As such, the detection and in-depth study of multimorbidity patterns would allow new preventive and management strategies. Comprehensive study of the association between chronic conditions may lead to a taxonomy system for the general population or specific subgroups of patients [45]. A reliable classification of patients could provide a more comprehensive approach to chronic-patient management, which in turn could lead to better health outcomes and a higher degree of health care system efficiency.

There is no generally accepted definition of multimorbidity pattern. In fact, studies on this topic do not present a definition, probably because this could be considered a self-explanatory concept. In spite of the absence of a clear definition, studies in this field have used a similar framework. Boyd et al defined it as "the specific and often multiple conditions that a person has (e.g., a person with depression, hypertension, chronic pain, and asthma), as opposed to a simple tally of the number of conditions that someone has" [46]. Prados-Torres et al considered multimorbidity as an "associative multimorbidity defined as the non-random association between diseases" [47].

Prados-Torres et al have recently published a systematic review on multimorbidity patterns with the aim of identifying studies focusing on this topic [47]. The review methodology excluded papers focusing on index diseases, those with less than 10 conditions available, and those lacking statistical techniques to prove that the associations were not produced by chance. Despite the urgent need for information in this area, only 14 papers were included after screening 6,601 references based on title and abstract. Among these, a high degree of heterogeneity was found regarding sample size, age, recruitment of participants, number of baseline conditions and statistical methods for the assessment of the patterns. For example, while some studies used complex techniques such as cluster analysis, others were limited to the assessment of observed/expected ratio of pair or triadic combinations [44,48]. These latter papers may add information regarding comorbidity but do not provide a global view of multimorbidity patterns.

Other studies have not taken into account individual relationships between conditions but rather the association between predetermined domains of diseases, such as the vascular domain or the psychological domain (which include several conditions) [49]. Studying how these domains associate with each other may be difficult and lead to misinterpretations since

this approach does not reflect the real individual associations between conditions. Other limitations arising from studies are the restriction to very elderly participants in some studies, small sample size, geographically limited setting (e.g., only rural participants), specific clinical settings (e.g., only hospitalized patients) or particular subgroups of populations (e.g., homeless, insured population, intellectual disabled, etc.) [45,50–54]. The importance of uniform methodology in the study of multimorbidity patterns has been highlighted in several systematic reviews [47,55,56]. In-depth analysis of multimorbidity may benefit from large-scale population samples, standardized definitions of the diseases considered and statistical methods capable of distinguishing statistically significant associations from spurious ones [37].

The growing interest in multimorbidity contrasts with the small number of studies in Spain, where only three studies have assessed the presence of multimorbidity patterns [37,52,57]. There are, however, some methodological concerns when interpreting their results since the studies by García-Olmos et al and the study by Prados-Torres et al included participants of 15 years old and over while the study by Formiga et al analyzed data on participants aged 85 years old and over. Since the prevalence of chronic conditions becomes relevant in adulthood, especially among those aged 40-50 years, it is important to assess the patterns in the Spanish general population including adults over 50 years old.

1.2.4. Impact of multimorbidity: need for deeper knowledge and specific management

Poor clinical outcomes have been observed in individuals with multimorbidity [58]. The negative impact of multimorbidity on clinical outcomes results in poor functional status and high mortality rates and accounts for 36 million deaths attributed to chronic, non-communicable diseases globally per year [59–62]. The consequences of multiple chronic conditions are poorly understood. While it seems clear than specific diseases may have a greater impact than others at various levels, additive impact may be a relevant factor. Furthermore, not only additive but synergic negative effect may be present, such as the associations found by Fultz et al between specific pairs of physical conditions and disability [63].

Costs associated with chronic conditions can reach up to 65% of total health expenditure in developed countries, as this is related to the use of a wide variety of health services [21,22,58]. For example, Nagl et al found a total annual cost of 6,862 € for patients with 10+ diseases compared with 1,250 € for participants with no diseases [21]. The relationship between

multiple chronic conditions and health costs is curvilinear, near exponential in some studies [22]. The Centers for Disease Control and Prevention analyzed American trends in healthcare utilization and highlighted the importance of various factors, especially the growing numbers of chronic patients [64].

High use of healthcare resources by multimorbidity patients may have, in turn, implications at a clinical level. Coordination becomes complex in patients with several co-occurring conditions, considering that the number of visits to various physicians for one single patient ranges from 1 to 14, in patients suffering from 1 to 5 or more conditions, respectively [65]. Moreover, these patients have a high pill burden, which may be responsible for interaction or adverse events, and the complexity of the diseases may also lead to further difficulties in coping with their own care [13]. There have been mixed results in studies trying to elucidate whether multimorbidity patients receive the appropriate care for their chronic conditions [13]. In that regard, the complexity of these patients is increasing while specialization in medicine has led to fragmentation in the care of patients [66]. The lack of integrated plans and guidelines for patients with co-occurring conditions is also related to current difficulties in following guidelines and giving clear instructions for self-care management [12,66]. Considering all these problems, recent policy efforts have focused on prevention and control of chronic diseases, highlighting the importance of better understanding of multimorbidity [19,67,68]. Therefore, there is a need for a broader approach, including research in multimorbidity, to develop comprehensive, realistic clinical guidelines that take the co-occurrence of conditions into account rather than focusing on individual diseases [69].

1.3. Chronic conditions and visual impairment

In the context of population aging, visual impairment has emerged as a growing concern in public health. Further research into the relationship between visual impairment and chronic medical conditions is needed.

1.3.1. Vision impairment in the elderly

Sensory functions are considered health domains of wellbeing by the International Classification of Functioning, Disability and Health (ICF) [70] (Figure 5). The ICF was published by the World Health Organization with the aim of providing a unified, standard framework for the description of health and health-related states, in which an individual's functioning is affected by the interaction between the health conditions and contextual factors [70]. In particular, the b2100 series in the ICF defines the visual acuity functions as

“seeing functions of sensing form and contour, both binocular and monocular, for both distant and near vision”.

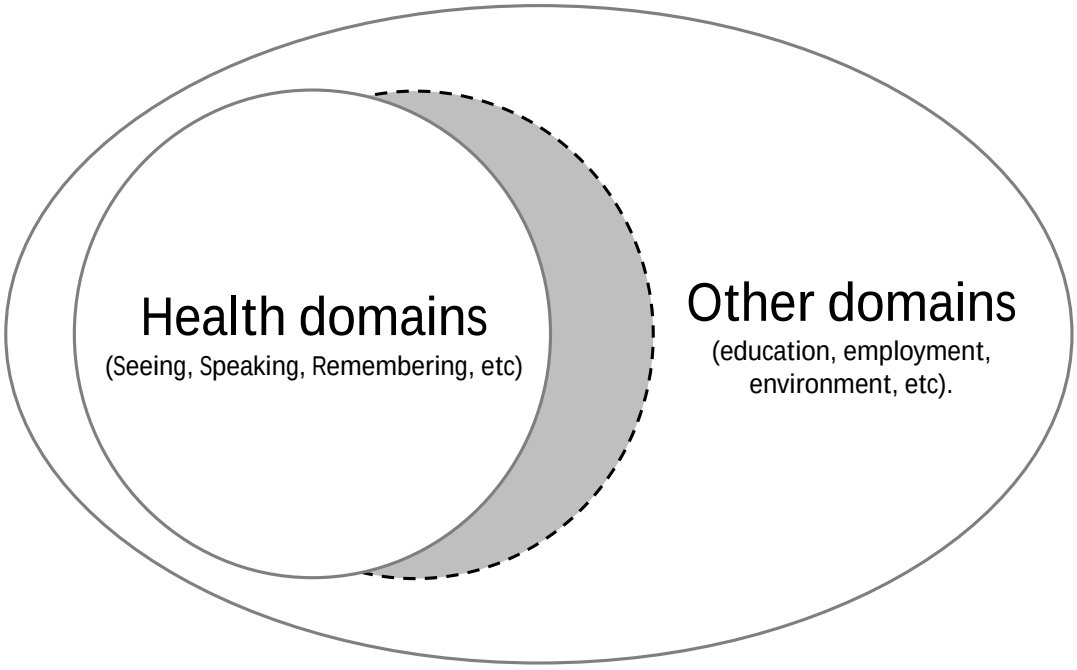

Figure 5. Health-related domains according to the International Classification Of Functioning, Disability And Health. Adapted from ICF (WHO, 2001). [70]

Visual impairment is associated with an increased risk of falling, activity limitations, higher healthcare utilization, lower quality of life, poorer social participation and increased mortality [71–78]. Low vision is commonly defined as a severe visual impairment with acuity lower than 6/18 and equal to or better than 3/60 in the better eye with best correction [79]. Although this represents a significant impairment, people affected with low vision are still potentially able to perform some activities for which sight is essential.

There is a strong association between aging and visual impairment. For example, 65% of people living with moderate or severe visual impairment and 82% of those with blindness are aged 50 years and over, while this group only represents about 20% of the world’s total population [80]. Specifically, it is known that prevalence of most visual disorders leading to visual impairment increases with age: cataract, Age-related macular degeneration (AMD), glaucoma, pathologic myopia and diabetic retinopathy [81,82]. The number of people with impaired vision is expected to increase over coming decades as a 2-fold increase in the population over 60 years old has been predicted between 2006 and 2050 [4,83]. Although most of these disorders can be treated, for instance through prescription of glasses, cataract surgery, or AMD intravitreal pharmacotherapy, permanent functional visual impairment can

appear in cases of no treatment or cases of delayed/unsuccessful treatment [84]. About 80% of all visual impairment could be avoided or cured, so there is a need to deepen understanding of the causes and factors underlying visual impairment to foster initiatives aimed at obtaining the best visual function [85].

1.3.2. Vision impairment and chronic physical conditions

Since multimorbidity and vision impairment are clearly related to the aging process and may lead to disability, lower quality of life, and greater use of healthcare services, it would be interesting to assess the possible association between the onset of chronic conditions and visual impairment. For instance, it is known that diabetes is associated with the onset of retinopathy [86]. In addition to diabetes, there is some evidence on the association of certain chronic conditions and visual impairment. For example, Li et al found a significant association between heart disease or stroke and visual impairment, although this was not the aim of the study and the analysis was made with Chi-Square test [72]. There is, however, very little information regarding the association between vision functioning and most common medical conditions at both individual and cumulative levels. For example, Lamoreaux et al presented descriptive data where the presence of non-ocular chronic conditions, coded as a single variable, showed a higher prevalence of visual impairment but no statistical analyses were performed [87]. Varma et al found that the number of number chronic conditions was related to unilateral or bilateral visual impairment, but the analysis was confined to Chi-squared test [88]. In some cases, multimorbidity is present in studies as a covariate and no information is available since both multimorbidity and visual impairment were considered independent variables [89,90].

1.3.3. Vision impairment and mental disorders

Some studies have assessed the association between certain mental disorders and visual functioning but further study is needed. Nyman et al performed a systematic review on quantitative studies assessing the association between mental disorders and visual impairment [91]. The search revealed nine studies on depression and eight studies on anxiety, with mixed results. The authors conclude that more research is required to clarify the association between mental disorders, such as depression and anxiety, and visual impairment. This review contained some limitations that should be pointed out:

- Inclusion of a specific ocular disease but no statistically significant differences in visual acuity with reference groups [92].

- Some studies focused on very specific ocular diseases, such as subfoveal choroidal neovascularization in which the effect of the treatment was assessed rather than the association between mental disorders and visual impairment [93].
- The search was limited to a short period (studies from 2001 to 2008).
- Number of results too limited to allow conclusions to be drawn.
- The unspecific assessment of some of the variables. For example, one study assessed depression with the single question: “Have you felt downhearted and blue during the last 4 weeks?” [88].
- Statistical limitations, such the lack of adjustment in some studies (e.g., chi-square test or descriptive information provided) hindering assessment of the association [88].

Due to the scarcity of available evidence and the limitations of some of the studies in the review, we conducted a systematic review on the association of visual functioning and mental health (restricted to depression and anxiety as these are the most prevalent mental disorders). Papers assessing the effect of ocular diseases without considering visual functioning, e.g., through visual acuity test measure, were not included. The search strategy was: ("visual loss" OR "vision loss" OR "low vision" OR "visual impairment" OR "vision impairment") AND ("depression" OR "depressive disorder" OR "anxiety"). Articles in English, with no time restriction, were selected. Age selection criteria were: study population groups of individuals over 50 years and studies with specific analysis of people aged over 50 years. Studies with other age selection criteria but reporting on a mean age over 55 years were also included. Abstracts were selected for further examination where they met criteria and the full article was then reviewed to determine whether it was suitable for inclusion. Non original articles and reviews were initially excluded. However, text reviews of these articles were used to identify additional articles. (Source: PubMed. Updated search: Date: 5th June 2014).

Table 2. Summary of previous studies on vision impairment and mental disorders.

Author (year)	Sample size	Age	Methodology	Vision assessment	Mental disorders instruments	Statistical association with	
						Depression	Anxiety
Bergdahl et al (2005) (94)	242	≥85	Cross-sectional population-based study	Near vision (ability to read words printed in 3-mm capital letter at reading distance)	Documented Medical diagnosis or GDS-15	YES	-
Brody et al (2001) (95)	151	≥60	Cross-sectional study from a randomized clinical trial (AMD patients)	a) Visual acuity (Snellen chart) b) Vision-related impact: SIPV (subjective) c) Vision-related functioning: NEI-VFQ (subjective)	SCID –IV	a) YES b) YES c) YES	-
Carriere et al (2013) (96)	4216	≥65	Cohort study of community-dwelling persons	a) Near vision: Parinaud scale. b) Distance vision: self-reported (ability to recognize a face at 4 m).	MINI diagnose of Major depressive disorder or CES-D score ≥16	a) NO b) YES	-
Chi et al (2005) (97)	917	≥60	Community-based cross-sectional study	Self-reported indicator regarding sight problems.	GDS-15	YES	-
Chou et al (2004) (98)	2003	≥60	Population-based cross-sectional study	Parciticipants' self-rate vision from 1 to 4. Then dichotomized. (0 =good and very good=0; 1 =and poor and almost-completely unable to see)	GDS-15	YES (NO for co-occurring vision-hearing impairment)	-
Chou et al (2008) (99)	3782	≥65	2-year population-based prospective observational study	Parciticipants' self-rate vision from 1 to 6. Then dichotomized. (0 =excellent, very good, and good; 1 = fair, poor, and legally blind)	CES-D	YES (NO for co-occurring vision-hearing impairment)	-
Chow et al (2004) (100)	245	≥65	Cross-sectional study with institutionalized patients	Visual loss categories (self-report)	GDS-15	YES	-
Eramudugolla et al (2013) (101)	662	≥70	Community-based cross-sectional study	a) High contrast Visual acuity test b) Low contrast visual acuity test	GADS	a) NO b) YES	a) NO b) YES
Evans et al (2007) (102)	13900	≥75	Population-based cross-sectional study	Visual acuity (Glasgow Acuity Chart at 3 m.)	GDS-15 (depression) GHQ-28 (anxiety)	YES	NO
Forsell et al (2000) (103)	894	$\bar{x}$=84	3 year longitudinal community-based study	Visual impairment (methodology not described)	DSM IV symptoms	NO	NO
Harris et al (2005) (104)	1164	≥65	2-year longitudinal, community-based study	A single question regarding vision (not specified)	a) GDS-15 - baseline b) GDS-15 - follow-up (2 years)	a) YES b) NO	-
Hayman et al (2007) (105)	391	≥75	Cross-sectional study from a clinical trial on fall prevention (adults with severe visual impairment)	a) Visual acuity - LogMAR chart b) VF-14 (subjective)	GDS-15	a) NO b) YES	-
Horowitz et al (2005) (106)	584	≥65	Cross-sectional analysis of a longitudinal community-based study. Participants with recent vision loss	Vision loss severity measured with the functional vision screening questionnaire	SCID	NO	-
Jongenelis et al (2004) (107)	333	≥55	Cross-sectional study with institutionalized population.	Visual acuity questionnaire (not specified)	GDS-30	NO	-
Kempen et al (2014) (108)	148	≥57	Cross-sectional study; community-living older participants. Persons with low vision compared with a reference sample (n=4792).	Participants with low vision were recruited when applying for low-vision rehabilitation services and compared with general population from the GLAS study	HADS-D, HADS-A	YES	YES

Table 2. Continuation

Kempen et al (2014) (109)	148	≥57	Cross-sectional study; community-living older participants. Persons with low vision compared with a reference sample (n=4792).	Participants with low vision were recruited when applying for low-vision rehabilitation services and compared with general population from the GLAS study	HADS-D	YES	-
Lamoureux et al (2009) (87)	76	$\bar{x}$=84	Cross-sectional study in three low-level residential care facilities	Visual acuity (E test chart; distance and near vision)	PHQ-9	NO	-
Li et al (2010) (72)	36348	≥65	Cross-sectional study of age-related eye diseases (AREDs) in the general population	Subjective visual impairment (2 questions assessing distance and visual impairment)	- PHQ-8 - Life time depression and anxiety were based on self-reported diagnosis	Not clear (visual impairment was related to AREDs, and these, in turn, to depression)	Not clear (visual impairment was related to AREDs, and these, in turn, to anxiety)
Lotery et al (2007) (110)	166	≥50	Cross-sectional study of neovascular AMD patients	Visual acuity from medical records	HADS	NO	NO
Lupsakko et al (2002) (111)	470	≥75	Cross-sectional, population-based study	Visual acuity (Snellen eye chart for distance and near vision). A combined variable was created.	DSM-IV checklist (major depression criteria)	NO	-
Mabuchi et al (2008) (112)	460	$\bar{x}$=67	Cross-sectional analysis of a prospective study with POAG patients	Visual acuity (LogMar chart)	HADS-D, HADS-A	Not clear (visual acuity was lower in POAG, and POAG was related to depression)	Not clear (visual acuity was lower in POAG, and POAG was related to depression)
Rovner et al (2002) (113)	51	$\bar{x}$=81	6-month prospective, cohort study of patients with recent-onset of bilateral AMD	a) Visual acuity: Snellen eye chart b) Functional vision screening questionnaire (subjective)	CES-D	a) NO b) YES	-
Stek et al (2004) (114)	500	≥85	Cross-sectional analysis, community-based population	Visual acuity test	GDS-15	NO	-
Tournier et al (2008) (115)	21995	≥65	Population-based, retrospective cohort	Previous diagnosis of visual impairment in the public medical services program	RAMQ medical services database	YES	-
Varma et al (2006) (88)	5377	$\bar{x}$=55	Population-based cross-sectional study	Visual acuity using ETDRS charts at 4 m.	Single question (downhearted and blue during the last 4 weeks)	YES	-
Wang et al (2014) (116)	10009	$\bar{x}$≥57	Community-based cross-sectional study	Visual acuity test at 4 m	EQ-5D	NO (only found in Indian subgroup)	NO (only found in Indian subgroup)
Weyerer et al (2013) (117)	3214	≥75	Cross-sectional, community dwelling elders	Self-report questions from the SIDAM instrument	- GDS-15	YES	-

This table summarizes the studies that have assessed, to date, the relationship between visual impairment and mental health (depression, anxiety). The last two columns report on the associations found between visual impairment and the mental variables: "Yes" indicates that an association was found, "No" that the association was not present, and "-" that there was no assessment with regard to that variable. List of acronyms: AMD: age-related macular degeneration; CES-D: Center for Epidemiological Studies-Depression Scale; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV; EQ-5D: European Quality of Life-5 Dimensions; ETDRS: Early Treatment Diabetic Retinopathy Study; GADS: Goldberg Anxiety and Depression Scale; GDS-15: 15-item Geriatric Depression Scale; GHQ: General Health Questionnaire; HADS: Hospital Anxiety and Depression Scale; MINI: Mini International Neuropsychiatric Interview; OVA: objective visual assessment; PHQ: Patient Health Questionnaire; POAG: primary open-angle glaucoma; RAMQ: Quebec administrative health database; SCID: Structured Clinical Interview for the DSM-IV; SIDAM: Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-infarct Dementia and Dementia of Other Etiology; SVA: subjective visual assessment.

By using the established criteria, we found 27 articles from the initial 407 results (Table 2). As expected, some articles could not be included in this list due to insufficient explanation of the visual variable, e.g., Al-Shammari et al [118] or because they assessed the effect of having one specific condition, e.g., cataracts, rather than assessing vision functioning, e.g., Tasi et al [119]. 19 of the selected papers assessed depression and 8 assessed both depression and anxiety. Mixed results were found with regard to depression, with 13 studies showing no association for all or some of the analyses performed. The number of studies with regard to anxiety was low compared with depression. We found some limitations in the studies included in the review that should be addressed in future research:

- Simple statistics tools such as Chi-squared test, Fisher's exact test or unadjusted regression models with regard to our variables [88,94,95,100].
- Unspecific questions or categories (e.g., can watch the TV clearly) [100].
- In some studies, near vision was assessed with or without glasses in the very elderly, 85 years and over, where the need for glasses due to presbyopia is very high [94]. Ideally, it should be with glasses.
- Incomplete description of the visual variable by explaining, for instance, that a standard visual acuity questionnaire was used when, in fact, the standard method to assess visual acuity would be a visual acuity test. In this case, no further explanation was given [97,107].
- Lack of consistency of variables in the same study. For example, Carriere et al used a visual acuity test for near vision and a self-reported measure for distance vision. In this case, we cannot determine whether the contrary results regarding near and distance visual impairment are caused by the distance effect or by the different approach used in the study for each distance [96].

1.3.4. Visual impairment and cognition

Finally, apart from chronic physical conditions and mental disorders, there is a need to study the association between cognitive functioning and vision impairment. There is some evidence highlighting the possible association between dementia and ocular changes. For example, Chang et al summarized eye changes in Alzheimer's disease, such as retinal microcirculation. Moreover, although tests such as contrast sensitivity may be useful, the available research does not suggest a clear relationship between visual acuity changes and Alzheimer's disease [120]. With regard to the specific association between visual impairment and cognitive functioning, results to date are mixed. Sloan et al found a statistically significant association between these variables but the effect was considered small [121].

Elliot et al found an association between near visual acuity, but not distance visual acuity, and cognitive functioning, which reinforces the need to study this association thoroughly, including distance and near vision [122]. In this context, as in mental disorders, research should also include subjective visual perception to provide a complete picture of the association.

1.4. Impact of chronic conditions on disability and quality of life

Health care policies aim to increase life span cost-effectively while maintaining quality of life and functional ability. There is still a need for deeper understanding of how chronic conditions impact on quality of life and disability.

1.4.1. Disability and quality of life in the elderly

Disability and quality of life are health outcomes which reflect the global health of the individual at various levels. Disability can be defined as 'long term limitations in major activities of daily living' and includes a wide range of activities such as eating, dressing, washing, walking, etc. [123]. This is an umbrella term that reflects problems in bodily function, task performance and participation in life situations [124]. Quality of life (QOL) is defined by the WHO as "*an individual perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns*" [125]. This is, consequently, a broad multidimensional concept that includes both positive and negative aspects of life, and constitutes a major issue in the elderly [126,127].

The World Health Organization has stated that about 15% of the global population experiences disability [128]. In Spain, there are 3.8 million disabled people [129]. Logically, the subgroup over 64 years suffers from the highest rate of disability, and this increases with age. At the age of 80, more than half of the Spaniards suffer from some kind of problem related to activities of daily living, which reaches 56.9% in the case of women in this age subgroup [7]. Interpretation of disability data has to be conducted with caution, since there might be great variability with regard to the methodology used when collecting the data. From a clinical and research perspective, several indexes (e.g. Katz index, Barthel index, Walton index) have been used to assess the performance of Activities of Daily Living (ADL) and Independent Activities of Daily Living (IADL) [130]. Moreover, global disability scores, such as the World Health Organization Disability Assessment Schedule, have been shown to

be useful at an epidemiological level [131]. This tool has the advantage of including a wide range of variables, including most of the variables of the aforementioned indexes.

Since QOL is a multidimensional term, national official data tend to be imprecise, providing data on the gross domestic product, the human development index, social satisfaction, poverty, social issues, health, etc. [132]. From a health perspective, several QOL measures have been prepared for assessment of the elderly population, such as the Elderly Quality of Life Index (EQOLI), the Quality of Life Scale for Elderly (QOLS-E) and the QHOQOL-OLD supplementary module for the WHOQOL for use with older adults [133]. These and other instruments need to take into account the concerns of this population but also the reduced capacity of the elderly to complete such questionnaires. Therefore, quality of life questionnaires for older adults should be as short as possible and, ideally, allow comparison with younger adults [133].

1.4.2. Burden of chronic conditions

Disability and quality of life are complex concepts, which are affected not only by health issues, but also social, economic or individual characteristics. Health-related factors that are thought to impact disability and quality of life are: chronic diseases, injuries, mental impairment, malnutrition, HIV and other communicable diseases [134]. In this context, chronic conditions have been presented as one of the leading causes of preventable morbidity and disability [128]. The EU Health Policy Forum has requested that "Disability-Adjusted Life Years" (DALYs) and "Quality Adjusted Life Years" (QALYs) should be part of the reflection process regarding the approach to population aging in Europe, highlighting the importance of the study of these concepts in the elderly [12].

With regard to research on the impact of chronic conditions on disability and quality of life, most studies have focused on the study of a single condition [135]. For example, Rozzini et al found an independent association between IADL and depression but no association was found with previous stroke, heart disease, cancer or Parkinson's disease in this cross-sectional study [136]. Lower quality of life and higher rates of disability have also been found in people with chronic diseases such as arthritis, diabetes or asthma whilst limited or controversial results have been found for other chronic conditions [137–142].

In other cases, the effect of chronic conditions on quality of life or disability has been assessed by using an index condition as a reference, so that assessment focused on the pair combinations of this index disease with other conditions [143–145]. This approach allows consideration of an additive, synergistic or substractive effect of these pair combinations.

However, since this approach only takes into account the pairs of an index disease, neither the majority of the combinations nor the cumulative effect are studied. Some recent studies have introduced a more comprehensive analysis including pairs, organ domains, or cumulative effects but there is still a need to increase knowledge of this topic [146–149].

Women suffer higher rates of disability than men. Several reasons have been put forward to explain this discrepancy [2]. First, differences in life expectancy lead to a higher number of older women in the population. Since disability rates increase with age, there is, consequently, a higher number of women with disability. Secondly, “healthy life expectancy” is similar between women and men, meaning that women spend these extra years with more disability than men. Thirdly, the fact that women suffer from higher rates of chronic conditions could be related to differences across gender. Although gender differences are known to exist with respect to disability, quality of life and chronic diseases, very little is known about the relationship between them [139,150,151]. Thus, future research on disability and quality of life should cover gender differences.

Finally, since most of the studies refer to index conditions, they are usually carried out in a clinical setting. Thus, a public health perspective is needed, focusing especially on the elderly, the age group most affected by multimorbidity. Understanding the factors that interact with disability and quality of life is essential to finding ways of assessing, preventing and dealing with these issues at a public health level.

Chapter 2
Hypothesis and objectives

HYPOTHESIS

In the context of population aging, many issues remain unclear with regard to multimorbidity in the Spanish older adult population. The specific hypotheses in this thesis dissertation are:

1. In the Spanish older adult population, there are some combinations of co-occurring chronic conditions, or multimorbidity patterns, which appear more frequently than would theoretically be expected by chance.

2. The presence of certain chronic physical conditions is associated with a higher frequency of mental disorders.

3. A greater impact of physical chronic conditions on mental health may be expected when several co-occurring chronic conditions are present.

4. Chronic physical conditions may impact greatly on visual impairment, with a more severe impact as conditions accumulate in individuals.

5. Mental disorders and cognitive impairment are associated with visual impairment, especially with subjective measures of visual performance.

6. Disability and quality of life are strongly related to the presence of several co-occurring conditions. A substantial increase in disability and decrease in quality of life is expected as the number of co-occurring conditions grows.

7. Gender differences are expected, with women suffering from higher rates of disability and lower quality of life for a specific condition or number of chronic conditions.

OBJECTIVES

The main objective of this thesis dissertation is to provide an insight into multimorbidity in the Spanish older adult population 50+. The specific objectives are:

1. To examine the distribution of chronic conditions and multimorbidity in the Spanish older adult population.

2. To assess the association between individual physical conditions (e.g., diabetes, angina) and the prevalence of mental disorders in the population over 50 years of age.

3. To evaluate the relationship between physical multimorbidity and the prevalence of mental disorders in the Spanish population over 50 years of age.

4. To study the individual and cumulative impact of chronic physical conditions on visual impairment in the population over 50 years old.

5. To analyze the relationship between visual impairment and the presence of mental disorders and cognitive impairment in the population over 50 years old.

6. To explore the individual and cumulative impact of chronic physical and mental conditions on quality of life and disability in the population over 50 years of age.

7. To examine general trends in quality of life and disability across gender in relation to the individual and cumulative effects of chronic conditions.

Chapter 3
Methods and results

Chapter 3
Paper 1

Multimorbidity Patterns in a National Representative Sample of the Spanish Adult Population

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Multimorbidity Patterns in a National Representative Sample of the Spanish Adult Population

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Abstract

Background: In the context of population aging, multimorbidity has emerged as a growing concern in public health. However, little is known about multimorbidity patterns and other issues surrounding chronic diseases. The aim of our study was to examine multimorbidity patterns, the relationship between physical and mental conditions and the distribution of multimorbidity in the Spanish adult population.

Methods: Data from this cross-sectional study was collected from the COURAGE study. A total of 4,583 participants from Spain were included, 3,625 aged over 50. An exploratory factor analysis was conducted to detect multimorbidity patterns in the population over 50 years of age. Crude and adjusted binary logistic regressions were performed to identify individual associations between physical and mental conditions.

Results: Three multimorbidity patterns rose: 'cardio-respiratory' (angina, asthma, chronic lung disease), 'mental-arthritis' (arthritis, depression, anxiety) and the 'aggregated pattern' (angina, hypertension, stroke, diabetes, cataracts, edentulism, arthritis). After adjusting for covariates, asthma, chronic lung disease, arthritis and the number of physical conditions were associated with depression. Angina and the number of physical conditions were associated with a higher risk of anxiety. With regard to multimorbidity distribution, women over 65 years suffered from the highest rate of multimorbidity (67.3%).

Conclusion: Multimorbidity prevalence occurs in a high percentage of the Spanish population, especially in the elderly. There are specific multimorbidity patterns and individual associations between physical and mental conditions, which bring new insights into the complexity of chronic patients. There is need to implement patient-centered care which involves these interactions rather than merely paying attention to individual diseases.

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Introduction

A two-fold increase in the worldwide population over 60 years old is expected between 2006 and 2050 [1]. Aging is associated with an exponential increase in multimorbidity. Two out of three people who have reached retirement age suffer from at least two chronic conditions [2,3]. Poor clinical and financial outcomes have been observed in individuals with multimorbidity [4]. The negative impact of multimorbidity on clinical outcomes results in poor functional status and high mortality rates, and accounts for 36 million deaths attributed to chronic, non-communicable diseases globally per year [5–8]. Associated costs due to chronic conditions reach 75% of total health expenditure, as it is related to the use of a wide variety of health services, such as physician consultation, hospitalization, medication, rehabilitation, long-term care or transportation [9,10].

When analyzing multimorbidity, most studies have focused on the link between co-occurring pairs of conditions or the mere descriptive counting of diseases [11,12]. There is a clear need to analyze cumulative interactions between diseases, although few studies have done so [13,14]. The study of multimorbidity patterns can lead to a deep understanding of multimorbidity. However, in some studies, the individual relationships between diseases were not taken into account but rather the interaction between predetermined domains of diseases, such as the vascular domain or the psychological domain [15]. Associations between these prefixed domains could affect the interpretation of the results since the individual associations between diseases are not assessed.

Current population aging trends have led to increasing interest in multimorbidity, resulting in some complex studies on the topic being published [2,13,16,17]. However, they mostly use small sample sizes, are restricted to very elderly participants, cover geographically limited areas or only included patients in primary care settings [2,13,18,19]. In this context, a recent systematic review concluded that there is need for a better description and understanding of multimorbidity [20]. In-depth analysis of multimorbidity may benefit from large-scale population samples, standardized definitions of the diseases considered and statistical methods capable of distinguishing statistically significant associations from spurious ones [18].

Multimorbidity includes both physical and mental conditions. Few studies have analyzed the link between them, or the joint effect of mental and physical conditions on the probability of severe disability [21–24]. The reasons for co-occurrence of physical and mental conditions are poorly understood. They may be related to functional disability, pathophysiological mechanisms or cognitive aspects associated with being ill [25]. In the elderly, the study of co-occurrence trends between physical and mental diseases is especially relevant as it is the population with the highest rates of multimorbidity. However, few efforts have been made to study these trends [2,26].

Recent policy efforts focus on prevention and control of chronic diseases, highlighting the importance of a better understanding of multimorbidity [27–29]. At a clinical level, current guidelines mostly focus on individual diseases, ignoring the co-occurrence of other conditions. The need for a broader approach has been stressed, including multimorbidity research, to develop clinical guidelines [30]. In this study, we aim to use a large general population survey to examine:

- The distribution of multimorbidity in the adult population.
- The multimorbidity patterns in the population over 50 years of age.
- The impact of individual physical conditions and multimorbidity on the prevalence of mental conditions in the population over 50 years of age.

Methods

Design

This article is based on data from the COURAGE Project, a cross-sectional study of the general non-institutionalized adult population reached through household interviews [31]. The original study included data on populations in three countries: Finland, Poland and Spain. The current analyses are based on data from the Spanish sample.

Sample and procedures

A stratified, multistage, clustered area probability method was used to select a representative sample of the adult population in Spain. The target group was a community-residing population over 18 years old. Distinct procedures were used to select three samples according to age: 18–49; 50–79; ≥80 years. The populations over 50 years and over 80 years old were oversampled as they were the principal target of the study. People with language barriers were not included in the study. Face-to-face structured interviews were conducted through Computer-Assisted Personal Interviewing (CAPI) at respondents' homes in 2011 and 2012. The survey protocol was originally designed in English and then translated into Spanish according to WHO translation guidelines for assessment instruments [32]. Lay interviewers were trained with the instruments prior to the administration of the survey. Quality assurance procedures were implemented during fieldwork [33]. The final response rate was 69.9%. At the beginning of the interview, the interviewer judged, subjectively, whether the respondent had cognitive difficulties that would prevent them from answering the questions. In the case of the presence of cognitive problems, a short version of the survey was administered to proxy respondents. Data from proxy respondents were not analyzed since they did not include the diagnoses of all physical and mental conditions. Thus, the final analysis consisted of 4,583 participants, once data from the 170 proxy respondents were eliminated.

Data collection

Sociodemographic data were obtained with regard to age, gender, education level, marital status, employment status, household income and urbanicity. Chronic physical conditions were assessed by asking the person whether they had received medical diagnosis and treatment during the previous 12 months for angina, arthritis, asthma, cataracts, chronic lung disease, diabetes, edentulism, hypertension or stroke. In addition, questions about specific symptoms were included to detect undiagnosed cases. Algorithms based on clinical symptoms were implemented based on the WHO's SAGE study, current clinical guidelines and reference publications [34–40]. The participant was considered to have a condition if they met at least one of the two previously established criteria for angina, asthma, arthritis, chronic lung disease, stroke or cataracts. Hypertension, diabetes and edentulism had no symptomatic algorithms since they are considered asymptomatic conditions. Previous 12-month mental morbidity (depression and anxiety) was assessed with an adapted version of the World Health Organization Composite International Diagnostic Interview (CIDI), according to DSM-IV criteria.

Statistical analysis

Unweighted frequencies, weighted proportions, means, confidence intervals and cross tabulations were used for descriptive analysis. The Chi-square test was applied to measure differences in the prevalence of chronic diseases, multimorbidity, number of diseases and sociodemographic variables across age or gender variables.

Multimorbidity patterns were analyzed using exploratory factor analysis in participants over 50 years old. Exploratory factor analysis is a statistical technique used to summarize the correlation among a series of variables, with the expected aim of understanding the underlying structure of the data. This method defines a set of underlying factors, in our case multimorbidity patterns, by estimating the relationship between the variables in each factor. Moreover, it allows distinct variables to be included in various factors. Firstly, a correlation matrix is needed to assess the correlation structure between the variables; chronic conditions in our study. The tetrachoric correlation matrix was used due to the dichotomous nature of the variables, so that it is assumed that diseases included in our analysis have a progressive course and are diagnosed when they reach a certain threshold [41]. By using the results of the tetrachoric correlation matrix, the factor analysis technique leads to a certain number of factors but a selection of the statistically relevant ones is needed. The number of factors extracted corresponded to those with an eigenvalue of at least 1.0 [2]. For every selected factor, there is a factor loading value corresponding to each of the variables. A specific condition was selected to form part of a pattern if its corresponding factor loading was above 0.25, which indicates a stronger association [2,18]. The Kaiser-Meyer-Olkin method was used to estimate the adequacy of

the sample in the factor analysis, whilst cumulative variance was determined to describe the variance of the diagnostic data explained by the pattern. An oblique rotation (Oblimin) was performed to allow a better interpretation of the analysis factor.

Crude and adjusted binary logistic regressions were used to examine the relationship between physical conditions/physical multimorbidity with depression and anxiety in participants over 50 years old. Adjusted models included age, gender, education level, marital status, urbanicity and number of physical conditions. Results are reported as unadjusted and adjusted odds ratios (OR) with 95% CI.

Weights were used in all analyses to adjust for differential probabilities of selection within households, and post-stratification weights to match the samples to population socio-demographic distributions. The statistical analyses took into account the complex sampling design except for multimorbidity patterns, as this analysis was not available in the statistical packages for complex samples. Analyses were performed using IBM SPSS statistics 19 and STATA version 12.

Ethics statement

The COURAGE study was approved by the partners' Ethics Committees: Ethics Review Committee Fundació Sant Joan de Déu, Barcelona, Spain and Ethics Review Committee, La Princesa University Hospital, Madrid, Spain. Written informed consent was obtained from the participants and all investigators proceeded according to the principles expressed in the Declaration of Helsinki.

Results

Participant characteristics

The study population consisted of 4,583 participants. Statistically significant differences were detected when comparing age groups (18–49; 50–64; ≥65 years) with regard to education level, gender, household income, marital status and employment status, but not for urbanicity (Table 1). Lower educational levels and household incomes were linked to older participants. A higher proportion of women was observed in participants over 65 years.

Chronic conditions and multimorbidity prevalence in the overall population

In the overall population, hypertension, arthritis and cataracts were the most common conditions with prevalences of 16.6%, 13.7% and 10.6%, respectively (Table 2). Depression was the most prevalent of the mental disorders assessed, with a prevalence of 9.0%. Multimorbidity occurred in 20.0% of the sample, whilst 4.8% of the participants suffered from four or more conditions (Table 3). Differences in the prevalences and multimorbidity were detected according to age and gender. Prevalence of individual conditions, multimorbidity and number of chronic conditions were higher in the population over 65 except for anxiety, which was not statistically significant. Women had higher rates of depression, cataracts, arthritis, anxiety, multimorbidity and overall number of chronic conditions. Women over 65 years old represent the population subgroup with the highest multimorbidity rate (67.3%). In this subgroup, hypertension, arthritis, cataracts and depression accounted for 53.8%, 45.7%, 43.1% and 18.0% of the participants, respectively.

Multimorbidity patterns in older adults

In the factor analysis, three factors were selected according to the results of the eigenvalues. The adequacy of the sample was considered acceptable with a KMO value of 0.70, and a cumulative variance of 39.5%. The first multimorbidity pattern included angina, asthma and chronic lung disease (cardio-respiratory factor). The second one included arthritis, anxiety and depression (mental-arthritis factor) (table 4). Finally, the third pattern included hypertension, angina, stroke, diabetes, cataracts, arthritis and edentulism (aggregate pattern). All conditions were related to at least one pattern. Angina and arthritis were both present in two multimorbidity patterns.

Association between physical and mental conditions in older adults

Table 5 shows the crude and adjusted logistic regression between physical and mental conditions in a sample of people over 50. For crude analysis, all physical conditions but stroke were associated with depression. Arthritis, angina, chronic lung disease and asthma still remained associated with depression after adjusting for covariates. With regard to the number of physical conditions, patients with two and those with three or more physical conditions were at higher risk of suffering from depression compared with participants without any physical conditions (adjusted OR: 2.24, CI: 1.33–3.74; adjusted OR 4.38, CI: 2.31–8.33). Crude logistic regression linked angina, edentulism and arthritis with anxiety. After adjusting for covariables, the association with angina remained statistically significant. Having three or more physical conditions was also related to suffering from anxiety (adjusted OR 5.23, CI: 1.76–15.53).

Discussion

The results of our study revealed three multimorbidity patterns in the population over 50 years old. The identification and analysis of these patterns is important as very high multimorbidity rates have been detected in this population group. Furthermore, relationships between certain physical and mental conditions have been detected, which is also important for better understanding and management of these diseases.

The first multimorbidity pattern, "cardio-respiratory", included angina, chronic lung disease and asthma. A recent systematic review found an increased risk of cardiovascular disease in COPD patients [42]. In fact, the presence of obstruction, restriction and respiratory symptoms have been found to be related to higher risk of cardiovascular disease, even after adjusting for other conditions [43]. In addition to having smoking as a common risk factor, the relationship between cardiovascular and chronic pulmonary diseases may involve systemic inflammation, oxidative stress, hypoxia or aging [43,44]. Atherosclerosis is thought to be closely connected to lipid metabolism but also to inflammation [45]. In COPD there is a pro-inflammatory systemic state which may exacerbate the atherosclerotic process and its consequent negative cardiovascular effects. Moreover, at the diagnostic level there is an overlap in symptoms in this pattern, such as shortness of breath or chest pain, which may be important in the management of these patients.

The second multimorbidity pattern, "mental-arthritis", includes depression, anxiety and arthritis. Anxiety and depressive disorders are known to be comorbid in many cases. The NESDA study found that 63% of patients with current anxiety disorders had a current depressive disorder and 81% had a lifetime depressive disorder [46]. Additionally, in the ESEMeD study, suffering from general anxiety disorder or panic disorder was clearly associated with a higher risk of major depression [47]. Our results, linking arthritis to psychiatric disorders, support the results found in the World Mental Health Surveys across 17 different countries where arthritis resulted in a higher risk of developing mood disorders and

Table 1. Description of the sample of the Spanish Cohort of the COURAGE study.

		Total sample (n = 4583)	18–49 years	50–64 years	≥65 years	p
Age (mean; se)		47.6 (0.3)	35.7 (0.3)	57.0 (0.1)	74.9 (0.1)	
Education (n; %)						<0.001
	No education	1269 (16.6%)	62 (6.5%)	311 (16.6%)	896 (46.7%)	
	Primary	1265 (24.9%)	190 (20.9%)	548 (32.8%)	527 (29.8%)	
	Secondary	1423 (39.3%)	474 (48.1%)	638 (35.4%)	311 (16.6%)	
	University+	625 (19.2%)	232 (24.5%)	263 (15.2%)	130 (6.8%)	
Gender (n; %)						0.006
	Male	2078 (49.4%)	435 (51.4%)	829 (47.7%)	814 (45.0%)	
	Female	2505 (50.6%)	523 (48.7%)	931 (52.3)	1051 (55.0%)	
Household income (n; %)						<0.001
	1st quintile	871 (22.5%)	185 (22.8%)	357 (23.2%)	329 (21.0%)	
	2nd quintile	804 (16.3%)	110 (12.9%)	268 (17.9%)	426 (25.0%)	
	3rd quintile	875 (20.0%)	160 (19.0%)	273 (17.1%)	442 (25.6%)	
	4th quintile	962 (22.8%)	217(23.5%)	370 (22.4%)	375 (21.0%)	
	5th quintile	624 (18.4%)	196 (21.8%)	303 (19.4%)	125 (7.4%)	
Marital status (n; %)						<0.001
	Single	667 (27.3%)	357 (39.2%)	187 (10.4%)	123 (6.8%)	
	Married	2777 (56.6%)	519 (53.1%)	1238 (71.1%)	1020 (54.2%)	
	Separated/divorced	342 (7.1%)	76 (7.2%)	196 (10.9%)	70 (3.4%)	
	widowed	797 (9.0%)	6 (0.5%)	139 (7.6%)	652 (35.7%)	
Urban pattern (n; %)						0.216
	Urban	3958 (84.8%)	820 (85.4%)	1523 (83.7%)	1615 (83.9%)	
	Rural	625 (15.2%)	138 (14.6%)	237 (16.3%)	250 (16.1%)	
Employment (n; %)						<0.001
	Working	1360 (46.2%)	543 (61.3%)	773 (47.5%)	44 (2.3%)	
	Retired	1387 (16.4%)	2 (0.2%)	183 (11.4%)	1202 (66.6%)	
	Other	1611 (37.4%)	342 (38.4%)	681 (41.2%)	588 (31.2%)	

SE = Standard Error.
Note = unweighted frequencies (n), and weighted means and proportions are displayed. Household income was divided into 5 quintiles. Education category 'no education' included those people that had never been to school or did not finish primary school. Marital status 'married' category included currently married or cohabiting. Employment 'other' category included training, homemakers, unemployed, voluntary work, health problems, caring for family, sick leave, no need to work, temporary time off and voluntary work.
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anxiety disorders [48]. Moreover, comorbid depression-anxiety was found to be more strongly associated with arthritis than single mental disorders, which also supports our results [49]. Even though the specific mechanism underlying this relationship still remains unclear, longitudinal data suggest that arthritis would predict the new onset of psychiatric disorders [50].

The third pattern, artificially named the "aggregate pattern", is a broader one including seven physical conditions. Angina, hypertension, diabetes and stroke are related through the metabolic syndrome. Cataracts may be involved in this pattern as it is influenced by diabetes but also has been linked to joint diseases [2]. The underlying mechanisms that may exist between joint diseases and cataracts are unclear. Adverse effects of glucocorticoid for the treatment of rheumatism could be partially responsible for the higher prevalence of cataracts in these patients. However, Falsarella et al (2013) found a higher risk of developing cataracts after adjusting for glucocorticoid intake in patients with arthritis [51]. Thus, it has been suggested that an increase in inflammatory modulators in rheumatic disorders may also be related to the onset of cataracts [51]. Heart diseases have also been associated with joint diseases, which supports this pattern, and may be linked through inflammatory pathways [2,18]. A systematic review found a relationship between the presence of edentulism with hypertension, coronary artery disease, diabetes, rheumatoid arthritis and osteoporosis [52]. It has been suggested that edentulism may be related to arthritis through an inflammatory pathway and with cardiovascular diseases through dietary or inflammatory causes [52].

Regarding the relationship between physical and mental conditions, asthma, angina, chronic lung disease and arthritis were associated with depression in the binary logistic regressions after adjusting for covariates. Only angina showed a clear association with anxiety after adjusting for covariates. These associations have been highlighted in previous studies [53–56]. There are some hypotheses to explain these findings. Firstly, arthritis, angina, chronic lung disease and asthma present with unpleasant symptoms such as joint pain, chest pain or shortness of breath, whereas cataracts, diabetes, hypertension, edentulism or stroke are mainly asymptomatic [25,57]. Moreover, these diseases may be linked to higher disability, leading to isolation or frustration [58]. Other

Table 2. Prevalence of 12-month physical conditions, mental disorders and multimorbidity according to age and gender.

	TOTAL	18–49 years		50–64 years		≥ 65 years		p (age)	p (sex)
		Men	Women	Men	Women	Men	Women		
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)		
Depression	9.0 (7.9–10.2)	5.2 (3.5–7.5)	9.0 (6.8–11.7)	8.4 (6.4–11.1)	15.2 (11.6–19.7)	5.1 (3.7–6.8)	18.0 (15.6–20.6)	<0.001	<0.001
Angina	2.8 (2.4–3.3)	0.4 (0.2–0.9)	0.5 (0.1–1.6)	5.3 (3.7–7.6)	2.4 (1.6–3.7)	10.1 (8.4–12.0)	8.5 (6.5–10.9)	<0.001	0.337
Cataracts	10.6 (9.9–11.4)	1.7 (0.9–3.3)	2.0 (1.1–3.5)	7.8 (6.4–9.6)	9.7 (8.0–11.7)	32.3 (29.2–35.6)	43.1 (39.9–46.5)	<0.001	<0.001
Asthma	4.8 (4.1–5.7)	3.6 (2.3–5.7)	4.2 (2.9–5.9)	3.6 (2.6–4.9)	5.0 (3.7–6.9)	7.1 (5.4–9.3)	8.8 (6.9–11.2)	<0.001	0.178
Hypertension	16.6 (15.5–17.7)	4.1 (2.4–6.7)	2.7 (1.5–4.7)	25.8 (22.9–29.0)	21.3 (18.2–24.7)	44.8 (40.7–48.9)	53.8 (50.6–56.9)	<0.001	0.066
Edentulism	9.0 (7.7–10.6)	3.2 (1.7–5.9)	2.5 (1.2–4.9)	9.2 (7.4–11.3)	7.3 (5.5–9.6)	24.9 (21.5–28.7)	31.0 (26.6–35.7)	<0.001	0.081
Diabetes	6.7 (6.0–7.5)	2.5 (1.5–4.2)	1.5 (0.7–3.1)	11.4 (9.3–14.0)	7.7 (5.8–10.1)	18.6 (16.1–21.5)	17.6 (15.4–20.1)	<0.001	0.219
Arthritis	13.7 (12.7–14.8)	3.2 (1.8–5.6)	7.7 (5.9–10.0)	10.9 (8.8–13.4)	25.3 (22.1–28.7)	20.4 (17.6–23.6)	45.7 (41.9–49.5)	<0.001	<0.001
Chronic Lung D	3.4 (2.8–4.0)	1.3 (0.6–2.8)	1.1 (0.6–2.3)	4.8 (3.4–6.7)	3.3 (2.3–4.8)	11.5 (9.1–14.6)	7.2 (5.7–9.1)	<0.001	0.100
Stroke	2.1 (1.7–2.6)	0.7 (0.3–1.9)	0.4 (0.1–1.2)	2.4 (1.4–4.0)	2.3 (1.4–3.8)	7.5 (5.2–10.7)	5.9 (4.2–8.3)	<0.001	0.509
Anxiety	1.1 (0.8–1.5)	0.8 (0.3–2.5)	1.0 (0.4–2.4)	1.2 (0.7–2.1)	2.4 1.6–3.5)	0.1 (0.1–0.8)	1.8 (1.1–2.8)	0.120	0.154
Multimorbidity	20.0 (18.8–21.2)	4.0 (2.7–5.9)	6.0 (4.2–8.4)	21.3 (18.2–24.6)	27.0 (23.2–31.3)	52.9 (48.7–57.0)	67.3 (64.6–70.0)	<0.001	<0.001

CI= Confident interval. Note= Weighted proportion and 95% Confident Intervals are shown. Anxiety included Generalised Anxiety Disorder and Panic Disorder. Multimorbility is defined as the presence of ≥ 2 physical or mental conditions. p(age) refers to statistical differences in the three groups of age; p(sex) refers to differences in gender, regardless the age group.

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explanations include the possible effects of pro-inflammatory cytokines, platelet activation, disturbances in the autonomic nervous system or hypothalamic-pituitary-adrenal axis dysfunction [53]. It should be noted that previous studies also found other relationships, i.e., diabetes with depression [49]. Further research is needed to assess the directionality of these effects and confirm other specific relationships. In addition to co-occurring pairs, the number of physical conditions was also associated with higher prevalence rates of depression and anxiety. The small amount of evidence that exists, is in agreement with our findings [13].

Multimorbidity was present in 20.0% of the overall adult population, consistent with results of about 20.3–30% from similar studies [59–61]. An increase in the prevalence of multimorbidity was associated with age, reaching 67.3% in women and 52.9% in

Table 3. Number of total, physical and mental conditions according to age and gender.

		TOTAL	18–49 years		50–64 years		> 65 years		p (age)	p (sex)
			Men	Women	Men	Women	Men	Women		
		% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)		
Total conditions									<0.001	<0.001
	0	58.7 (56.9–60.6)	78.1 (73.9–81.9)	76.4 (72.6–79.8)	47.5 (43.7–51.3)	45.2 (41.2–49.2)	20.7 (17.0–25.0)	9.9 (8.6–11.4)		
	1	21.3 (19.7–23.0)	17.91 (14.5–22.0)	17.7 (14.5–21.4)	31.3 (28.1–34.7)	27.8 (23.5–32.6)	26.4 (23.6–29.4)	22.8 (20.3–25.5)		
	2	9.7 (9.0–10.6)	3.36 (2.2–5.0)	4.37 (3.0–6.3)	11.1 (9.15–13.4)	15.4 (12.6–18.7)	24.4 (21.2–28.0)	23.8 (21.2–26.6)		
	3	5.4 (4.9–6.1)	0.64 (0.2–2.1)	0.90 (0.3–2.7)	5.5 (4.1–7.4)	6.4 (4.8–8.6)	15.9 (132–19.1)	21.1 (18.6–24.0)		
	≥4	4.8 (4.3–5.4)	0	0.69 (0.2–2.1)	4.7 (3.1–7.0)	5.2 (4.13–6.60)	12.6 (10.4–15.1)	22.4 (19.7–25.4)		
Physical conditions									<0.001	<0.001
	0	62.5 (60.7–64.2)	82.5 (78.5–85.8)	81.3 (78.1–84.1)	49.5 (45.7–53.3)	51.6 (46.5–56.5)	20.8 (17.1–25.1)	10.8 (9.5–12.3)		
	1	20.1 (18.6–21.7)	14.9 (11.7–18.8)	16.4 (13.7–19.6)	31.6 (28.5–34.9)	26.6 (23.4–30.0)	27.4 (24.7–30.4)	24.2 (21.9–26.8)		
	2	8.5 (7.8–9.3)	2.2 (1.4–3.7)	1.36 (0.76–2.4)	10.8 (8.8–13.3)	12.9 (10.6–15.8)	24.1 (20.9–27.6)	26.4 (23.7–29.3)		
	≥3	8.9 (8.3–9.6)	0.4 (0.1–1.7)	0.91 (0.4–2.4)	8.05 (6.1–10.6)	8.9 (7.3–10.9)	27.8 (24.1–31.7)	38.6 (35.6–41.6)		
Mental conditions									<0.001	<0.001
	0	90.5 (89.3–91.7)	94.1 (91.6–95.8)	90.7 (87.8–93.0)	91.3 (88.6–93.4)	84.3 (79.7–88.0)	94.8 (93.0–96.2)	81.6 (78.9–84.0)		
	≥1	9.5 (8.4–10.7)	5.9 (4.2–8.4)	9.3 (7.0–12.2)	8.7 (6.6–11.4)	15.7 (12.0–20.3)	5.2 (3.8–7.0)	18.4 (16.0–21.1)		

CI= Confident interval. Note= Weighted proportion and 95% Confident Intervals are shown.

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Table 4. Factor score for each condition in participants over 50 years.

Condition	Factor1	Factor2	Factor3
Angina	**0.40**	0.24	**0.33**
Cataracts	0.20	0.20	**0.48**
Asthma	**0.80**	0.10	0.05
Hypertension	0.15	0.10	**0.50**
Edentulism	0.09	0.10	**0.37**
Diabetes	0.17	0.01	**0.50**
Arthritis	0.24	**0.27**	**0.28**
Chronic Lung Disease	**0.79**	0.15	0.07
Stroke	0.09	0.04	**0.46**
Anxiety	0.07	**0.78**	−0.01
Depression	0.24	**0.76**	0.12

Factor 1 (cardio-respiratory); Factor 2 (mental-arthritis); Factor 3 (aggregate pattern).
Note = Factor scores ≥0.25 are highlighted.
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men over 65 years, which is also comparable to results described in recent reviews [20,62]. In fact, most studies on multimorbidity in the literature focus on the old or very-old population, the subgroups with the highest rates. However, in our study, multimorbidity was found in more than 20% of the subgroup between 50–64 years. This result highlights the importance of using a broader age framework to achieve deeper understanding of the phenomenon. Multimorbidity was also related to gender, with women suffering from more overall conditions, physical conditions and mental conditions than men. These results are consistent with most multimorbidity studies [20]. Once examined individually, depression, cataracts and arthritis showed statistically significant differences across gender. These results show that special attention should be paid to the management of elderly women in health care as they are more prone to develop multimorbidity and the effect on the quality of life is more severe than men [63].

Regarding the individual prevalence of chronic physical conditions, hypertension, arthritis and cataracts were the most prevalent physical conditions in older adults, affecting over 40% in the 65+ subgroup. The high prevalence of cardiovascular-related conditions should be highlighted, as they are the second cause of premature mortality in Spain after cancer [64]. Edentulism was present in 24.9% of men and 31.0% of women over 65 years. This value is relevant because edentulism is related to poorer quality of life but also represents an indicator of the adequacy of the national oral health care system [65,66]. Chronic lung disease and asthma also showed significant increases across age. There is controversy regarding the prevalence of asthma in the elderly. It is assumed that asthma prevalence may decrease with age but some studies suggest underdiagnosis due to diagnostic difficulties [67,68]. Our results are consistent with the last national health survey in Spain, which showed the highest prevalence of asthma in the population over 85 years [69]. The overlapping symptoms between late onset asthma and chronic obstructive pulmonary disease could be partially present in our results, so that caution is required when interpreting this outcome. According to our results, older adults and elderly people often suffer from chronic diseases which can be partially prevented, e.g., diabetes, angina, chronic lung disease, so that further efforts must be made in our country to develop appropriate national health policies. Once established, tight control of some of these conditions is associated with better health outcomes. Thus, it is essential to maximize their management, which is especially important due to the high prevalence of conditions such as diabetes or hypertension.

Interesting results arise when comparing the prevalence of mental conditions across age. No difference was found in the prevalence of anxiety when comparing age groups. Prevalence of

Table 5. Logistic regression models to predict mental conditions.

	Depression model		Anxiety model	
	OR crude (95%CI)	AOR (95%CI)	OR crude (95%CI)	AOR (95%CI)
Asthma	**2.79 (2.01–3.85)**	**1.86 (1.31–2.64)**	1.60 (0.67–3.84)	0.90 (0.37–2.19)
Cataracts	**1.99 (1.47–2.68)**	1.32 (0.95–1.83)	1.64 (1.00–2.71)	1.17 (0.66–2.08)
Angina	**2.55 (1.80–3.61)**	**2.01 (1.40–2.90)**	**3.96 (2.25–6.98)**	**3.39 (1.84–6.22)**
Edentulism	**1.43 (1.09–1.88)**	0.96 (0.74–1.24)	**1.73 (1.03–2.91)**	1.38 (0.80–2.37)
Hypertension	**1.50 (1.10–2.03)**	0.92 (0.70–1.21)	1.51 (0.85–2.68)	0.94 (0.50–1.77)
Chronic Lung Disease	**3.18 (2.21–4.59)**	**2.66 (1.84–3.86)**	2.09 (0.87–5.10)	1.49 (0.56–3.97)
Stroke	1.77 (0.97–3.24)	1.30 (0.72–2.34)	0.84 (0.34–2.10)	0.59 (0.22–1.57)
Arthritis	**2.70 (1.98–3.69)**	**1.62 (1.19–2.21)**	**2.64 (1.52–4.59)**	1.46 (0.73–2.90)
Diabetes	**1.73 (1.23–2.43)**	1.25 (0.85–1.84)	0.82 (0.44–1.54)	0.54 (0.28–1.04)
Number of physical conditions				
0	1	1	1	1
1	1.29 (0.68–2.46)	1.41 (0.75–2.67)	1.21 (0.43–3.43)	1.43 (0.48–4.25)
2	**1.95 (1.14–3.35)**	**2.24 (1.33–3.74)**	2.13 (0.76–5.97)	2.94 (1.00–8.67)
3+	**3.72 (1.94–7.13)**	**4.38 (2.31–8.33)**	**3.50 (1.31–9.33)**	**5.23 (1.76–15.53)**

OR = Odds Ratio; 95%CI = Confident interval; AOR = Adjusted Odds Ratio; in bold, statistically significant ($p<0.05$).
Note = Adjusted models included age, gender, education level, marital status, urban pattern and number of physical conditions.
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depression showed differences across the three groups. There is controversy surrounding the prevalence of mental disorders in the elderly. The ESEMeD study found a decrease in the prevalence of 12-month anxiety and mood disorders across age [70]. In the ESEMeD study, prevalence of any mental disorder in the last 12 months was lower than in our case, 9.8% in the 50–64 group and 5.8% in the 65+ group. By contrast, some studies have shown much higher prevalence [71,72]. These differences may be explained in various ways. It has been pointed that the elderly have to cope with several issues which could be related to higher incidence of mental disorders: cognitive decline, sensory impairment, decrease in social relationships, cessation of activity and change of status [73]. Economic recession is also a factor related to the current higher prevalence of mental disorders in Spain [74]. On the other hand, differences in prevalence may be partially explained by different approaches according to the diagnosis scheme of the study. This especially affects the results in the elderly because lower prevalence of depression may be due to the excessive cognitive requirements of the diagnostic interviews, and the attribution of the symptoms to physical illnesses in the elderly [75]. This problem will be addressed with new tools such as a specific version of the CIDI for the population over 65, currently in preparation [76].

Our study has several limitations. The cross-sectional nature of the study may affect the interpretation of the results, so that longitudinal studies are needed to better understand associations. This kind of study does not distinguish between age effects and cohort effects. Moreover, study of multimorbidity would benefit from standardized inclusion and conceptualization of diseases [2,20]. Studies with a similar number but different conditions assessed make comparison difficult [2]. Some studies have taken a broader approach using the Expanded Diagnosis Clusters (EDC) of the ACG® system, which are more exhaustive but complex to conduct outside the clinical settings or in the case of poor integration between health care levels [18]. A higher number of included conditions logically results in a higher proportion of multimorbidity [20]. Furthermore, when counting diseases, they were scored independently of severity, which can also introduce bias. In our case, the selection of the conditions was done according to the World Health Organization's SAGE study. SAGE's inclusion criteria focused on a limited number of conditions impacting significantly on health that is general enough to work with across countries. There is, however, a need to include the diagnosis of dementia in future studies, as it is a common condition in the elderly which has a considerable impact on quality of life, disability and health care resources. The self-reported data collection method could also bias the results. However, this effect may be minor since previous studies have found a good correlation between self-reported and medical-record diagnoses [77,78]. Finally, our study did not include the medication list or the current number of drugs taken by the patient. Since multimorbidity is intimately related to polypharmacy and inappropriate drugs can have a considerable impact on the health of the elderly, it would be useful to include this information in future studies.

Conclusions and Future Research

The results of our study contribute to a deeper understanding of chronic conditions and multimorbidity at various levels. In Spain, multimorbidity reaches a considerable prevalence in adults over 65 years old, but also in patients between 50 and 64. Several multimorbidity patterns and relationships between physical and mental conditions have been detected. The knowledge of these associations could lead to an integrated approach to patients suffering from these diseases, both from a clinical and a public health perspective. Patients with multimorbidity are more complex and require a greater number of medical consultations. Integrated plans taking multimorbidity into account represent an opportunity to improve the cost-efficiency of the health care system. Further research with a longitudinal approach is needed to assess the causes, the clinical impact and the financial implications of these associations.

Author Contributions

Conceived and designed the experiments: JP JMH MM JLA. Performed the experiments: NG BO MVM JP JMH MM JLA. Analyzed the data: NG BO JP MVM JMH. Contributed reagents/materials/analysis tools: NG BO JP MVM JMH. Wrote the paper: NG BO MVM JP JMH MM JLA. Critically revised the paper and approved the final version to be published: NG BO MVM JP JMH MM JLA.

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Chapter 3
Paper 2

Visual Impairment and Multimorbidity in a Representative Sample of the Spanish Population

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Visual impairment and multimorbidity in a representative sample of the Spanish population

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Abstract

Background: In the context of population aging, visual impairment has emerged as a growing concern in public health. However, there is a need for further research into the relationship between visual impairment and chronic medical conditions in the elderly. The aim of our study was to examine the relationship between visual impairment and three main types of co-morbidity: chronic physical conditions (both at an independent and additive level), mental health and cognitive functioning.

Methods: Data were collected from the COURAGE in Europe project, a cross-sectional study. A total of 4,583 participants from Spain were included. Diagnosis of chronic medical conditions included self-reported medical diagnosis and symptomatic algorithms. Depression and anxiety were assessed using CIDI algorithms. Visual assessment included objective distance/near visual acuity and subjective visual performance. Descriptive analyses included the whole sample (n = 4,583). Statistical analyses included participants aged over 50 years (n = 3,625; mean age = 66.45 years) since they have a significant prevalence of chronic conditions and visual impairment. Crude and adjusted binary logistic regressions were performed to identify independent associations between visual impairment and chronic medical conditions, physical multimorbidity and mental conditions. Covariates included age, gender, marital status, education level, employment status and urbanicity.

Results: The number of chronic physical conditions was found to be associated with poorer results in both distance and near visual acuity [OR 1.75 (CI 1.38-2.23); OR 1.69 (CI 1.27-2.24)]. At an independent level, arthritis, stroke and diabetes were associated with poorer distance visual acuity results after adjusting for covariates [OR 1.79 (CI 1.46-2.21); OR 1.59 (CI 1.05-2.42); OR 1.27 (1.01-1.60)]. Only stroke was associated with near visual impairment [OR 3.01 (CI 1.86-4.87)]. With regard to mental health, poor subjective visual acuity was associated with depression [OR 1.61 (CI 1.14-2.27); OR 1.48 (CI 1.03-2.13)]. Both objective and subjective poor distance and near visual acuity were associated with worse cognitive functioning.

Conclusions: Arthritis, stroke and the co-occurrence of various chronic physical diseases are associated with higher prevalence of visual impairment. Visual impairment is associated with higher prevalence of depression and poorer cognitive function results. There is a need to implement patient-centered care involving special visual assessment in these cases.

Keywords: Epidemiology, Chronic conditions, Multimorbidity, Visual impairment, Low vision, Mental health, Cognitive functioning, Elderly

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Background

Visual impairment is related to higher morbidity, increased risk of falling, activity limitations, lower quality of life, poor social participation and increased mortality [1-8]. Low vision is a state of moderate or severe visual impairment defined as a visual acuity lower than 6/18 and equal to or better than 3/60 in the better eye with best correction [9]. Even though this represents significant impairment, people affected with low vision are still potentially able to perform some activities for which sight is essential. The relevance of vision to health status has led the World Health Organization to recently introduce vision and other sensory functions as health domains in the International Classification of Functioning, Disability and Health (ICF), a unified framework for a description of health that highlights the interaction between health conditions and contextual factors [10].

In industrialized countries, the main causes of low vision and blindness are age-related macular degeneration (AMD), glaucoma, cataracts, pathologic myopia and diabetic retinopathy. The prevalence of all these disorders increases with age [11,12]. In fact, about 65% of people who are visually impaired are aged 50 and older, while this group only represents about 20% of the world's population [13]. Since a 2-fold increase in the population over 60 years old is expected between 2006 and 2050, the number of people with impaired vision is expected to increase in the future [14,15]. Although some of these disorders can be treated, for instance through cataract surgery or AMD intravitreal pharmacotherapy, permanent functional visual impairment can appear in cases of delayed or inefficacious treatment [16].

Aging is also clearly associated with the onset of chronic physical and mental conditions and an increase in multimorbidity [17,18]. According to a recent review, between 55% and 98% of the elderly population suffer from multimorbidity [19]. Some particular associations have been identified between chronic physical conditions and vision disorders, such as diabetes and retinopathy [20]. However, there is very limited information on the relationship between visual functioning and most common medical chronic conditions at both the independent and additive levels. Sensory impairment has also been linked to psychological and social problems. Mild or moderate visual impairment in adults have been found to be associated with mental distress, depression, anxiety, suicide risk, interpersonal sensitivity and hostility [2,21-26]. Most of these studies have focused on depression and little is known about the relationship between sensorial impairment and other psychiatric conditions, such as anxiety, especially in the elderly. Moreover, there is evidence of an association between visual impairment and dementia [27,28]. To date, however, research focusing specifically on the association between visual impairment and cognitive functioning has showed mixed results [29-33]. Determining the relationship between visual impairment and chronic conditions through a comprehensive approach might contribute to the development of optimal patient-centered care to the elderly.

We used a large general population survey to examine:

- The relationship between physical multimorbidity and visual impairment in the population over 50 years old.
- The relationship between visual impairment and mental health (depression and anxiety) in the population over 50 years old.
- The relationship between visual impairment and cognitive functioning in the population over 50 years old.

Methods

Design

The COURAGE in Europe project is a cross-sectional household survey of a representative sample of the non-institutionalized adult population conducted in Finland, Poland and Spain [34]. Data from the Spanish sample are analyzed in the current study.

Sample and procedures

A representative sample of the adult population in Spain was selected using a stratified multistage clustered area probability method. The target group was a community-residing population over 18 years. Three samples were selected according to age: 18–49; 50–79; ≥80 years. The 50+ and 80+ subgroups were oversampled as they were the main target of the study. People with language barriers were excluded. From July 2011 to May 2012, face-to-face structured interviews were conducted through Computer-Assisted Personal Interviewing (CAPI) at respondents' homes. The survey protocol was translated from English into Spanish according to WHO translation guidelines for assessment instruments [35]. Lay interviewers were trained before administration of the survey. Quality assurance procedures were implemented during fieldwork [36]. The final response rate was 69.9%. The main reason for non-response was that the house was unoccupied or that the members of the household were elsewhere (seasonal vacancy, other residence). The interviewer judged whether the respondent had cognitive problems at the beginning of the interview. If cognitive difficulties were evident, a short version of the survey was obtained from proxy respondents. Data from proxy respondents were not analyzed since visual assessment and diagnosis of chronic physical conditions and mental disorders were not performed in the proxy interviews. Therefore, once the 170 proxy respondents had been eliminated, the final analysis consisted of 4,583 participants. This sample was used

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for initial descriptive purposes. The final analysis consisted of 3,625 participants over 50 years old since this subgroup suffers from significant prevalence of chronic conditions and visual impairment compared with younger populations.

Data collection

Sociodemographic information included age, gender, marital status, education level, employment status and urbanicity. With regard to chronic physical conditions, participants were asked whether they had received lifetime medical diagnosis and treatment during the previous 12 months for angina, arthritis, asthma, chronic lung disease, diabetes, edentulism, hypertension and stroke. Moreover, algorithms based on clinical symptoms were implemented to detect undiagnosed cases. These were based on the WHO's SAGE study, current clinical guidelines and reference publications [37-43]. In the case of meeting at least one of the two previously established criteria, the respondent was considered to have angina, asthma, arthritis, chronic lung disease or stroke. Hypertension, diabetes and edentulism are asymptomatic conditions so no symptomatic algorithm was used. Previous 12-month major depressive disorder and anxiety disorders (including Generalized Anxiety Disorder and Panic Disorder) were assessed with an adapted version of the World Health Organization Composite International Diagnostic Interview (CIDI), according to DSM-IV criteria [44]. Cognitive functioning results were calculated from five performance tests in distinct domains: learning and short-term memory (word list immediate and delayed recall from the Consortium to Establish a Registry for Alzheimer's Disease), attention and working memory (digit spans forward and backward from the Weschler Adult Intelligence Scale) and language (animal naming task) [45,46]. All performance tests were scored according to standard practice for each test. A global score was calculated using the sum of the standardized score on each item, with a lower score indicating worse cognitive functioning [47]. Analogous methodology for computing this score with the same tests has previously been used in the WHO's SAGE and COURAGE studies [47,48]. In our case, we also standardized results by level of education. Results were later transformed into a binary variable for analysis purposes. Objective visual acuity was measured by the interviewer with a "tumbling E" chart [49]. To assess distance vision, an appropriate chart was placed 3 meters from the participant. Visual acuity was registered using the metric visual acuity scale, through which patients were classified into one of the following groups: visual acuity less than 3/60, 3/60-6/60, 6/60-6/18 and more than 6/18. To demonstrate the visual acuity required by a line in the chart, the participant had to detect at least three of the four letters in the line. Distance VA was measured initially for the left eye and subsequently for the right eye. Analog procedures were conducted to assess near vision, with a specific appropriate chart that was held by the participant at a comfortable distance. For near vision, participants were classified as: unable to see the largest sized letter (<N48), able to see largest size (N48), able to see medium size (N20), able to see the smallest size (N8). All the measures were taken in daily-life light conditions with the participant's usual visual correction. The interviewer made sure that the vision chart was well lit with natural or indoor lighting and that the surface did not reflect glare. Visual performance for distance and near vision was taken from the eye with the better visual acuity results. Subjective visual acuity was assessed through two questions: a) *In the last 30 days, how much difficulty did you have in seeing and recognizing an object or a person you know across the road (from a distance of about 20 meters)?*; b) *In the last 30 days, how much difficulty did you have in seeing and recognizing an object at arm's length (for example, reading)?* Five answers were permitted: none, mild, moderate, severe, extreme.

Statistical analysis

Unweighted frequencies, weighted proportions, means, confidence intervals and cross tabulations were applied for descriptive analyses. The Chi-square test was used to measure differences in visual performance, prevalence of chronic diseases, multimorbidity, number of conditions and sociodemographic variables across age and gender.

Crude and adjusted binary logistic regressions were used to examine the association between chronic physical conditions and visual performance in participants over 50 years (n = 3625). Results are reported as Odds Ratio (OR) with 95% CI. Adjusted models included age, gender, education level, marital status, urbanicity, and all chronic physical conditions. For the analyses regarding the relationship between multimorbidity and visual performance, adjusted models included age, gender, education level, marital status, urbanicity, and number of chronic conditions. Analogous procedures were used to examine the association between visual acuity and the variables related to mental health (depression, anxiety) and cognitive functioning. In this case, adjusted models included age, gender, education level, marital status, urbanicity and all chronic physical conditions. Visual acuity variables were transformed into binary variables for the logistic regression. Objective distance visual acuity was classified as "poor" (lower than 6/18) or "good" (equal or better than 6/18). Objective near visual acuity was classified as "good" (able to read the smallest letters) or "poor" (other cases). Subjective visual acuity with no or mild problems was considered "good", and "poor" in the case of more serious problems. The Kappa inter-agreement test

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was performed for objective and subjective visual performance. The association was considered as fair (Kappa: 0.3206; Standard Error: 0.0118) [50]. For this reason, objective and subjective visual performance were taken into account separately in the logistic regression relating vision and mental health.

The statistical analyses took into consideration the complex nature of the sample design. Weights were used in all analyses to adjust for differential probabilities of selection within households, and post-stratification weights to match the samples to population socio-demographic distributions. Analyses were performed using IBM SPSS statistics 19.

Ethics statement

The COURAGE study was approved by the partners' Ethics Committees: Fundació Sant Joan de Déu Ethics Review Committee, Barcelona, Spain and La Princesa University Hospital Ethics Review Committee, Madrid, Spain. Written informed consent was obtained from the participants. All investigators worked according to the principles expressed in the Declaration of Helsinki.

Results

Participant characteristics

The study population consisted of 4,583 participants. A summary of the sociodemographic data is available in Table 1. Age differences are statistically significant in educational level, marital status and employment. As expected, prevalence of physical multimorbidity, chronic physical conditions and mental conditions increased with age, except for anxiety (Table 2). Cognitive functioning below median per group was: a) 18–49 years: 48.5% (CI: 44.9-52.1); b) 50–64 years: 65.2% (CI: 61.5-68.7); c) 65+: 83.1% (CI: 80.9-85.0).

In the overall adult population, a decrease in distance visual acuity was observed across age groups (Table 3). No gender differences were observed. For near visual acuity, the worst results were found in the elderly and in women. In the population aged over 65 years, only 33.8% of the women and 43.0% of the men achieved highest near visual acuity. Age and gender differences were also present in the subjective perception of distance and near vision problems. Elderly women was the group with the poorest results.

Table 1 Description of the sample of the Spanish Cohort of the COURAGE study

	Total sample (n = 4583)	18-49 years (n = 958)	50-64 years (n = 1760)	≥65 years (n = 1865)	*p*
Age (mean; SE)	47.6 (0.3)	35.7 (0.30)	57.0 (0.1)	74.9 (0.1)	
Education (n; %)					<0.001
No education	1269 (16.64%)	62 (6.53%)	311 (16.62%)	896 (46.70%)	
Primary	1265 (24.93%)	190 (20.92%)	548 (32.81%)	527 (29.84%)	
Secondary	1423 (39.29%)	474 (48.07%)	638 (35.42%)	311 (16.61%)	
≥University	625 (19.14%)	232 (24.48%)	263 (15.15%)	130 (6.80%)	
Gender (n; %)					0.006
Male	2078 (49.4%)	435 (51.35%)	829 (47.70%)	814 (44.95%)	
Female	2505 (50.6%)	523 (48.65%)	931 (52.30)	1051 (55.04%)	
Marital status (n; %)					<0.001
Single	667 (27.3%)	357 (39.18%)	187 (10.39%)	123 (6.75%)	
Married	2777 (56.6%)	519 (53.12%)	1238 (71.10%)	1020 (54.18%)	
Separated/divorced	342 (7.1%)	76 (7.21%)	196 (10.86%)	70 (3.36%)	
Widowed	797 (9.0%)	6 (0.49%)	139 (7.64%)	652 (35.72%)	
Urbanicity (n; %)					0.216
Urban	3958 (84.78%)	820 (85.40%)	1523 (83.69%)	1615 (83.93%)	
Rural	625 (15.22%)	138 (14.60%)	237 (16.31%)	250 (16.07%)	
Employment (n; %)					<0.001
Working	1360 (46.21%)	543 (61.34%)	773 (47.47%)	44 (2.28%)	
Retired	1387 (16.43%)	2 (0.24%)	183 (11.35%)	1202 (66.56%)	
Other	1611 (37.36%)	342 (38.41%)	681 (41.18%)	588 (31.16%)	

SE = Standard Error.
Note = unweighted frequencies (n), and weighted means and proportions are displayed. Household income was divided into 5 quintiles. Education category 'no education' included those people that had never been to school or did not finish primary school. Marital status 'married' category included currently married or cohabiting. Employment 'other' category included training, homemakers, unemployed, voluntary work, health problems, caring for family, sick leave, no need to work, temporary time off and voluntary work.

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Table 2 Prevalence of 12-month chronic physical conditions, mental disorders and multimorbidity according to age

	Total	18-49 years	50-64 years	≥65 years	*p* (age)
Angina	2.84 (2.44-3.29)	0.4 (0.2-0.9)	3.8 (2.9-4.9)	9.2 (7.9-10.7)	<0.001
Asthma	4.83 (4.11-5.67)	3.9 (2.9-5.1)	4.3 (3.5-5.4)	8.1 (6.7-9.7)	<0.001
Hypertension	16.55 (15.48-17.68)	3.4 (2.3-5.0)	23.4 (21.3-25.7)	49.7 (47.4-52.0)	<0.001
Edentulism	9.03 (7.67-10.60)	2.8 (1.6-5.0)	8.2 (6.8-9.9)	28.3 (25.0-31.8)	<0.001
Diabetes	6.66 (5.95-7.45)	2.0 (1.3-3.0)	9.5 (7.9-11.3)	18.1 (16.2-20.1)	<0.001
Arthritis	13.72 (12.66-14.84)	5.4 (4.2-7.0)	18.4 (16.4-20.6)	34.3 (31.8-36.9)	<0.001
Chronic Lung D	3.35 (2.83-3.95)	1.2 (0.7-2.1)	4.0 (3.1-5.1)	9.1 (7.7-10.8)	<0.001
Stroke	2.13 (1.71-2.64)	0.5 (0.3-1.2)	2.4 (1.6-3.5)	6.6 (5.3-8.3)	<0.001
Depression	8.97 (7.88-10.19)	7.0 (5.5-8.8)	12.0 (9.8-14.5)	12.2 (10.6-13.9)	<0.001
Anxiety	1.09 (0.77-1.54)	0.9 (0.5-1.7)	1.8 (1.3-2.5)	1.0 (0.7-1.6)	0.120
Number of physical conditions					
0	64.4 (62.7-66.1)	82.8 (80.3-85.0)	53.0 (49.4-56.5)	19.9 (17.9-22.1)	<0.001
1	21.3 (19.9-22.7)	15.3 (13.2-17.7)	29.7 (27.3-32.3)	31.5 (29.7-33.4)	<0.001
2	8.1 (7.5-8.8)	1.4 (0.9-2.2)	10.3 (8.8-12.1)	26.3 (24.2-28.5)	<0.001
≥3	6.2 (5.6-6.8)	0.5 (0.2-1.2)	7.0 (5.8-8.3)	22.3 (20.1-24.7)	<0.001

Note = Weighted proportion and 95% Confidence Intervals are shown. Anxiety included Generalized Anxiety Disorder and Panic Disorder.

Association between physical health and visual acuity

Table 4 shows the crude and adjusted logistic regression odds ratios for the association between visual acuity and physical medical conditions in individuals over 50 years old (n = 3,625). In the crude analysis, all chronic physical conditions except chronic lung disease were associated with worse distance visual acuity. In the adjusted model, arthritis, stroke and diabetes were still associated with worse distance visual acuity after adjusting for other covariates (OR 1.79 [CI 1.46-2.21]; OR 1.59 [CI 1.05-2.42]; OR 1.27 [1.01-1.60] respectively). Similar results were found in the analysis of near visual acuity, although only stroke resulted in a higher odds of worse visual acuity (OR 3.01 [CI 1.86-4.87]) after adjusting for covariates. The number of concurrent chronic physical conditions was associated with an increased odds of worse visual acuity for both near and distance vision. In the adjusted model for distance visual acuity, patients with three or more chronic physical conditions had the highest odds (OR 1.75 [CI 1.38-2.23]). Similar results were found with regard to the number of chronic physical conditions and near visual acuity. The highest OR was associated with having three or more chronic diseases (OR 1.69 [CI 1.27-2.24]).

Association between visual acuity and variables related to mental health and cognition

After adjusting for covariates, subjective distance visual acuity and subjective near visual acuity were revealed to be associated with depression (OR 1.61 [CI 1.14-2.27]; OR 1.48 [CI 1.03-2.13]) (Table 5). No association was found in any visual acuity variable with regard to anxiety in the logistic model adjusting for covariates. For cognition, objective distance visual acuity, objective near visual acuity, subjective distance visual acuity and subjective near visual acuity were associated with lower cognitive performance in the adjusted model (OR 1.27 [CI 1.02-1.59]; OR 1.51 [CI: 1.28-1.85]; OR 1.43 [CI 1.00-2.06]; OR 2.40 [CI 1.52-3.71])

Discussion

Our study found a clear relationship between suffering from various co-occurring chronic physical conditions and poorer distance and near visual performance. Independently, arthritis and stroke were associated with poor visual acuity. With regard to mental health, poor subjective visual acuity was associated with depression. No association was found with anxiety. Both objective and subjective poor VA were associated with worse cognitive performance.

To date, this is the first study that has analyzed the association between suffering from co-occurring physical conditions and the odds of visual impairment, highlighting the additive effect of chronic conditions. After adjusting for covariates, our results show an increasing odds of poor distance and near visual acuity according to the number of chronic physical conditions. Since multimorbidity affects a large proportion of the adult and elderly population, this may be a common risk factor for visual impairment. This is especially important as visual impairment has been related to poorer results in quality of life and disability [3,6,51]. The underlying mechanism in this relationship is unknown. By analogy with frailty, in which accumulation of deficits increases vulnerability to adverse

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Table 3 Vision acuity results across age and sex groups

	TOTAL	18-49 years		50-64 years		> 65 years		p (age)	p (sex)
		Men	Women	Men	Women	Men	Women		
Objective DVA								<0.001	0.113
≥6/18	79.7 (76.3-82.8)	81.6 (76.0-86.1)	86.2 (82.2-89.4)	83.2 (79.8-86.1)	79.7 (75.2-83.7)	69.4 (64.3-74.0)	62.5 (57.7-67.1)		
6/60	16.7 (13.9-20.0)	17.0 (12.6-22.4)	11.9 (8.9-15.6)	15.1 (12.3-18.3)	17.7 (14.2-21.9)	21.9 (18.3-26.1)	25.3 (21.6-29.5)		
3/60	2.9 (2.3-3.8)	1.4 (0.5-3.9)	1.6 (0.8-3.2)	1.7 (1.0-2.9)	2.3 (1.5-3.7)	7.0 (5.1-9.4)	9.3 (7.4-11.7)		
<3/60	0.6 (0.4-0.9)	0.1 (0.0-0.7)	0.3 (0.1-1.6)	0.1 (0.0-0.4)	0.2 (0.1-0.5)	1.7 (1.0-3.0)	2.8 (1.8-4.5)		
Objective NVA								<0.001	<0.001
Smallest letter	68.8 (66.4-71.1)	84.7 (81.0-87.99	80.0 (76.5-83.1)	59.6 (55.8-63.3)	53.7 (49.1-58.3)	43.0 (38.0-48.1)	33.8 (30.1-37.6)		
Medium letter	28.6 (26.5-30.9)	14.5 (11.5-18.2)	18.6 (15.6-22.0)	38.1 (34.4-41.9)	43.4 (39.2-47.8)	50.8 (46.0-55.5)	57.9 (53.6-62.1)		
Large letter	2.1 (1.6-2.7)	0.5 (0.2-1.7)	1.4 (0.6-2.9)	2.1 (1.3-3.3)	2.3 (1.4-3.8)	5.1 (3.9-6.8)	5.9 (4.5-7.7)		
Not large letter	0.5 (0.3-0.8)	0.2 (0.0-1.4)	0	0.2 (0.1-0.8)	0.5 (0.2-1.4)	1.1 (0.5-2.4)	2.5 (1.5-4.1)		
Subjective DVA								<0.001	<0.001
None	87.8 (86.3-89.3)	93.2 (89.7-95.6)	93.4 (90.9-95.3)	89.9 (87.2-92.0)	83.9 (80.4-86.8)	78.5 (74.8-81.8)	67.5 (62.8-71.9)		
Mild	8.3 (7.1-9.6)	5.4 (3.4-8.5)	5.0 (3.4-7.2)	8.2 (6.2-10.9)	12.0 (9.5-15.1)	14.1 (11.6-16.9)	17.0 (13.9-20.6)		
Moderate	2.8 (2.3-3.5)	0.8 (0.2-3.4)	1.4 (0.8-2.6)	1.5 (0.9-2.5)	3.2 (2.2-4.5)	5.7 (4.2-7.6)	10.7 (8.8-13.1)		
Severe	1.1 (0.8-1.4)	0.6 (0.2-1.5)	0.2 (0.2-0.2)	0.4 (0.2-1.1)	1.0 (0.5-1.9)	1.8 (1.1-2.9)	4.7 (3.5-6.3)		
Subjective NVA								<0.001	0.506
None	89.2 (87.7-90.6)	93.1 (89.7-95.4)	96.2 (94.5-97.3)	88.3 (85.5-90.6)	85.7(82.0-88.8)	81.4 (77.7-84.7)	70.5 (65.6-74.9)		
Mild	8.0 (6.8-9.4)	5.4 (3.4-8.6)	3.2 (2.1-4.8)	8.6 (6.6-11.2)	11.4 (8.7-15.0)	13.3 (10.8-16.3)	19.9 (16.4-24.1)		
Moderate	2.2 (1.7-2.9)	1.0 (0.3-3.5)	0.6 (0.3-1.6)	2.8 (1.7-4.6)	2.6 (1.7-3.8)	4.4 (3.1-6.3)	7.3 (5.6-9.4)		
Severe	0.5 (0.4-0.8)	0.5 (0.2-1.4)	0	0.3 (0.1-0.9)	0.3 (0.1-0.8)	0.8 (0.4-1.7)	2.3 (1.5-3.5)		

DVA = distance visual acuity; NVA: near visual acuity. NOTE = Subjective visual assessment results were related to problems: none, mild problems, moderate problems, severe problems. Weighted proportion and 95% Confident intervals are shown; *p*(age) refers to statistical differences in the three age groups; *p*(sex) refers to differences in gender, with of the age group; subjective visual acuity is assessed as vision problems mentioned by the patient.

outcomes, the co-occurrence of various chronic conditions could be related to a higher risk of visual impairment [52]. People with several chronic conditions, such as cardiovascular conditions, diabetes or arthritis, may have cumulative risk due to vascular, neurodegenerative, biochemical or inflammatory pathways. Some of these relationships have been studied independently in some conditions. For example, diabetes is related to cataracts and diabetic retinopathy, and arthritis has been associated with a higher risk of cataracts [20,53,54]. However, it is known that not only diabetes but also hypertension and hypercholesterolemia are risk factors for diabetic retinopathy so, in this case, cumulative effects are possible [55,56].

Stroke was associated with a high odds of distance and near visual impairment (OR: 1.59 [CI 1.05-2.42]; OR: 3.01 [CI 1.86-4.87]). It is known that stroke is related to a range of visual sequelae, such as low vision, hemianopia, quadrantanopia and motility disorders, but little information is available at an epidemiological level [57]. Low vision may be due to vascular pathology or other ocular abnormalities [58]. Rowe et al. found that up to 92% of stroke survivors have some form of visual impairment [57]. Our results support this relationship and highlight the need for visual assessment after stroke. We also found a higher odds of distance visual impairment in respondents with arthritis. The relationship between arthritis and vision loss is poorly understood and may also be multifactorial. Firstly, extra-articular arthritis symptoms may include uveitis, ulcerative keratitis, scleritis, severe Sjögren syndrome and other conditions directly associated with vision loss [59,60]. Moreover, medication for arthritis such as corticoids or chloroquine/hydroxicloroquine have been associated with an increased prevalence of glaucoma, cataracts or retinopathy [61-64]. There is, however, no clear evidence on the relationship between osteoarthrosis and visual impairment. At an epidemiological level, there are few data on this issue but it has recently been suggested that there is a higher risk of eye diseases in patients with joint diseases [65]. Finally, individual odds of distance

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Table 4 Association between chronic physical conditions and poor visual acuity

	DVA (OR)	DVA (AOR)	NVA (OR)	NVA (AOR)
Angina	1.57 (1.17-2.11)	1.12 (0.84-1.51)	1.43 (1.07-1.91)	1.07 (0.78-1.48)
Asthma	1.42 (1.04-1.95)	1.02 (0.72-1.44)	1.38 (0.99-1.93)	1.04 (0.70-1.54)
Hypertension	1.28 (1.08-1.52)	0.87 (0.73-1.04)	1.51 (1.23-1.78)	1.10 (0.94-1.28)
Edentulism	1.70 (1.33-2.18)	1.12 (0.89-1.43)	1.74 (1.42-2.14)	1.16 (0.96-1.41)
Diabetes	1.59 (1.28-1.98)	1.27 (1.01-1.60)	1.22 (0.86-1.75)	1.15 (0.86-1.52)
Arthritis	2.30 (1.92-2.75)	1.79 (1.46-2.21)	1.63 (1.33-1.98)	1.16 (0.97 -1.40)
Chronic Lung D	1.38 (0.99-1.93)	1.02 (0.74-1.42)	1.34 (0.90-2.02)	1.06 (0.70-1.60)
Stroke	1.87 (1.24-2.83)	1.59 (1.05-2.42)	3.53 (2.18-5.73)	3.01 (1.86-4.87)
Number of physical conditions				
1	1.67 (1.35-2.08)	1.32 (1.07-1.63)	1.63 (1.38-1.94)	1.33 (1.13-1.57)
2	1.95 (1.51-2.51)	1.30 (1.00-1.67)	2.06 (1.64-2.60)	1.43 (1.13-1.81)
≥3	2.83 (2.23-3.58)	1.75 (1.38-2.23)	2.64 (2.00-3.48)	1.69 (1.27-2.24)

DVA = distance visual acuity; NVA: near visual acuity; OR = Odds Ratio; AOR = Adjusted Odds Ratio.
Note = Results with 95% Confidence interval. In bold, statistically significant ($p < 0.05$). AORs are based on logistic regression model including all medical conditions, age, gender, educational level, marital status, and urbanicity. For number of physical conditions, the adjusted models included number of physical conditions, age, gender, educational level, marital status, and urbanicity.

visual impairment was increased in diabetic patients, as expected. However, this association was slight and was not found in the case of near visual acuity, distance subjective visual acuity and near subjective visual acuity. We hypothesize that adjusting by the time from the onset of diabetes could impact the results with diabetes but this information was not available in our study.

With regard to mental health, our results show a clear association between visual impairment and depression. Although visual impairment and depression have been associated in working age adults [66], there is controversy on this topic in older adults [2,22,24,25,67,68]. Variability in the studies arises with regard to the type of visual assessment used, including objective visual acuity, medical-record review, presence of age-related eye-disease or vision-loss severity with functional screening. Besides objective measures, the need for measures that accurately assess the degree of visual impairment experienced by the person has been highlighted [69,70]. Self-experienced visual loss may be important as this could lead to disability, functional decline, and communicative and social isolation [66,71-74]. In our case, we tested both objective and subjective visual acuity to analyze the nature of their relationships with depression and other mental conditions. We found a stronger association between depression and subjective visual impairment, which highlights the importance of the self-perceived impairment. In fact, the Health Care Policy and Research Cataract Surgery Guidelines suggest that one important indication for cataract surgery may be the degree of functional disability rather than objective visual assessment alone [75,76]. The differing results in objective and subjective visual impairment with regard to depression could be influenced by the negative perception that these patients may have about themselves. Anxiety showed no association with visual acuity, corroborating previous studies in adults and the elderly [21,23,24,77-79]. There is, however, some controversy as higher rates of anxiety have been observed in populations with some ocular conditions [2,80]. Our study adds valuable information regarding anxiety because there are relatively few studies on this subject and in most cases they did not have a clear definition of anxiety. Other less-specific variables were used, such as concern about blindness. Moreover, our study deals with objective and subjective visual impairment, providing a general evaluation of the impact of visual performance on anxiety. The relevance of our results is reinforced by the fact that we have used the CIDI questionnaire, a comprehensive, standardized interview that

Table 5 Association between poor visual acuity and variables related to mental health and cognitive functioning

	Depression (OR)	Depression (AOR)	Anxiety (OR)	Anxiety (AOR)	Cognition (OR)	Cognition (AOR)
Distance VA	1.64 (1.27-2.12)	1.25 (0.97-1.61)	0.90 (0.47-1.71)	0.74 (0.39-1.40)	1.47 (1.17-1.86)	1.27 (1.02-1.59)
Near VA	1.39 (1.01-1.93)	1.10 (0.78-1.53)	0.97 (0.55-1.73)	0.83 (0.43-1.64)	1.72 (1.46-2.02)	1.51 (1.28-1.85)
Subjective distance VA	2.80 (2.10-3.74)	1.61 (1.14-2.27)	2.15 (1.14-4.04)	1.47 (0.71-3.04)	2.05 (1.44-2.90)	1.43 (1.00-2.06)
Subjective near VA	2.40 (1.74-3.30)	1.48 (1.03-2.13)	0.42 (0.09-1.93)	0.27 (0.05-1.36)	2.96 (1.92-4.55)	2.40 (1.52-3.71)

VA = visual acuity; OR = Odds Ratio; AOR = Adjusted Odds Ratio.
Note = Adjusted models included age, gender, education level, marital status, urbanicity and all chronic physical conditions. Results with 95% Confidence interval. In bold, statistically significant ($p < 0.05$).

has demonstrated particular usefulness in epidemiological and cross-cultural studies [81]. By using the CIDI, our results can be compared with those of other studies using the same approach.

Finally, cognitive functioning was found to be associated with distance and near visual impairment, at both objective and subjective levels. The strongest relationship was observed in subjective near visual impairment. Mixed results have previously been found with regard to visual performance and cognitive functioning in the elderly population [29-33,82].

Simulated visual impairment has shown cognitive slowing in adults, especially in the elderly [83,84]. Moreover, other studies have found a clear relationship between visual performance and cognitive disorders such as Alzheimer's and Parkinson's disease [85-87]. The interaction between vision and cognition is not fully understood. On the one hand, visual loss could lead to deprivation of sensory input, leading to cerebral structural or functional changes. On the other hand, a common physiological pathway could be involved. A loss of retinal ganglion cells and impairment of the ventral and dorsal pathways in patients with Alzheimer's disease has been described [85,88]. Besides the etiopathogenic implications of the association between vision and cognition, this interaction should be highlighted because coexisting visual and cognitive impairment has been related to a higher risk of disability [89].

Our study has several limitations. Cross-sectional studies identify associations but do not allow cause and effect relationships to be determined. Moreover, age effects may not be distinguished from cohort effects. Longitudinal studies are needed to confirm these results. Multimorbidity research would benefit from standardized inclusion and definition of diseases [65]. In some cases, the Expanded Diagnosis Clusters adapted of the ACG® system have been used, an exhaustive method that is complex to apply outside the clinical setting and where poor integration of health care levels exists [17]. It is known that a higher number of conditions results in a higher proportion of multimorbidity [19]. For our study, the choice of chronic conditions was made according to the SAGE study, focusing on a limited number of conditions that are highly prevalent in the general population and constitute major causes of disability. This methodology allows the work to be conducted across countries. Self-reported data could affect the results, although this would be minimal as acceptable correlation between self-reported and medical-record diagnosis has been found [90,91]. With respect to vision itself, future studies should include binocular visual acuity assessment and other visual tests such as contrast sensitivity and glare disability. Another limitation is the fact that some differences could arise when using distinct subjective strategies in the visual assessment, which could affect the results [92]. Moreover, since visual impairment becomes more frequent in advanced ages, participants in their fifties could potentially skew the results of the analyses. Consequently, we performed a sensitivity analysis with participants over 65 years which showed similar results compared with the results of the global sample (50 years and over). Finally, poorer results in cognitive functioning may appear in patients with vision loss when the tests include vision tasks [93,94]. In our study, only the verbal memory tests included a reading part. However, the interviewer read the words aloud if the respondent had reading difficulties, so this bias may be minimized.

Conclusion

The results of our study contribute to a deeper understanding of visual impairment and its relationship with chronic physical conditions and mental disorders. There seems to be a clear association between a higher number of co-occurring chronic physical conditions and poorer results in distance and near visual functioning. Elderly patients with multimorbidity would benefit from extra eye-care and this would also improve the efficiency of the health care system. At an independent level, suffering from stroke and arthritis is highly associated with poorer results in visual functioning. The presence of these conditions could be triggers for visual impairment. With regard to mental health, poor subjective but not objective visual functioning is closely related to depression, highlighting the importance of subjective perception in depression. Since poor cognition has also been related to poor visual functioning, it would be advisable to monitor mood and cognitive functioning in people suffering from visual disorders.

Competing interests

None of the authors have any proprietary interests or conflicts of interest related to this submission.
This submission has not been published anywhere previously and it is not simultaneously being considered by any other publication.

Authors' contributions

NG: Participated in the database management, drafted the paper, carried out the statistical analyses and worked on the interpretation of data. He also gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. BO: Participated in the acquisition of data, database management, critical revision of the paper, and carried out the statistical analyses. She also gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EL: Participated in the database management and critical revision of the paper. She also gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MVM: Participated in the study design, database management, statistical support and critical revision of the paper. She also gave final approval of the version to be published and agreed to be accountable for all aspects of the

work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MM: Participated in the acquisition of data, database management and critical revision of the paper. She also gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JLA: Participated in the study design, acquisition of data, interpretation of data and critical revision of the paper. He also gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JMH: Participated in the study design, acquisition of data, interpretation of data and critical revision of the paper. He also gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Chapter 3
Paper 3

Impact of Multimorbidity on Disability and Quality of Life in the Spanish Older Population

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Impact of Multimorbidity on Disability and Quality of Life in the Spanish Older Population

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Abstract

Background: Population aging is closely related to high prevalence of chronic conditions in developed countries. In this context, health care policies aim to increase life span cost-effectively while maintaining quality of life and functional ability. There is still, however, a need for further understanding of how chronic conditions affect these health aspects. The aim of this paper is to assess the individual and combined impact of chronic physical and mental conditions on quality of life and disability in Spain, and secondly to show gender trends.

Methods: Cross-sectional data were collected from the COURAGE study. A total of 3,625 participants over 50 years old from Spain were included. Crude and adjusted multiple linear regressions were conducted to detect associations between individual chronic conditions and disability, and between chronic conditions and quality of life. Separate models were used to assess the influence of the number of diseases on the same variables. Additional analogous regressions were performed for males and females.

Results: All chronic conditions except hypertension were statistically associated with poor results in quality of life and disability. Depression, anxiety and stroke were found to have the greatest impact on outcomes. The number of chronic conditions was associated with substantially lower quality of life [β for 4+ diseases: −18.10 (−20.95,−15.25)] and greater disability [β for 4+ diseases: 27.64 (24.99,30.29]. In general, women suffered from higher rates of multimorbidity and poorer results in quality of life and disability.

Conclusions: Chronic conditions impact greatly on quality of life and disability in the older Spanish population, especially when co-occurring diseases are added. Multimorbidity considerations should be a priority in the development of future health policies focused on quality of life and disability. Further studies would benefit from an expanded selection of diseases. Policies should also deal with gender idiosyncrasy in certain cases.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. The COURAGE project is a collaborative effort between several European institutions and the World Health Organization. The questionnaire is based on the WHO's SAGE study, in order to allow future comparisons across countries. SAGE data is already available on the WHO's webpage. Researchers can contact them and SAGE team provides the data requested, as in other WHO's public databases. Data from the COURAGE will be available soon with a similar system. Until then, all the relevant data related to this paper will be available without restriction from the COURAGE study team in Spain (beatriz.olaya@pssjd.org) for consultation. This database covers the definition of "minimal dataset" by Plos One, to reach the conclusions drawn in the manuscript and to replicate the reported study findings in their entirety.

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Background

Population aging has gradually increased over the last years, with projections suggesting a two-fold increase in the worldwide population over 60 years old between 2013 and 2050 [1]. By then, the proportion of older people is expected to be double that of children in developed countries [2]. This demographic trend has led the European Commission to identify population aging as a crucial challenge in the 21st century [3].

The aging process is associated with the onset of chronic conditions so that two thirds of elderly citizens in Europe suffer from multimorbidity, defined as the presence of at least two co-occurring conditions [4,5]. Poor clinical and financial outcomes have been observed in patients with multimorbidity [6]. Chronic, non-communicable diseases are the biggest cause of death in high-income countries; responsible for more than 70% of deaths in 2008 [7]. Costs associated with chronic conditions have been estimated at 75% of total health expenditure, which is related to a wide range of health services such as hospitalization, medication, physician consultation, transportation, rehabilitation or long-term care [8,9]. Health care in this context should aim to increase life span in a cost-efficient way while maintaining quality of life and the abilities required to perform daily-life activities [10].

Disability and quality of life are health outcomes which reflect the global health of the individual at various levels [11–14]. Disability is an umbrella term that reflects problems in bodily function, task performance and participation in life situations [12]. Quality of life is a broad multidimensional concept that includes both positive and negative aspects of life, and constitutes a major issue in the elderly [13,14]. When analyzing the impact of chronic conditions on disability and quality of life, most studies have focused on the study of a single condition [15]. Lower quality of life and higher rates of disability have been found in people with chronic diseases such as arthritis, diabetes or asthma whilst limited or controversial results have been found for other conditions [16–21]. In other cases, the effect of chronic conditions on quality of life or disability has been assessed by using an index condition as a reference and the effects when considering the combination with other conditions [22–24]. This implies, for example, assessing how a specific index disease, such as diabetes, interacts with other conditions, e.g., diabetes and hypertension, diabetes and asthma. Comorbidity, or the study of these specific pairs of conditions, was introduced by Feinstein and adds very valuable information but also has its limitations [25]. Using this approach, an additive, synergistic or subtractive effect of these pair combinations can be explored. However, by using comorbidity pairs, neither the majority of all possible combinations nor the cumulative effects are studied, so that another, more comprehensive approach including the most relevant combinations is needed.

Multimorbidity is a relatively new concept that considers the co-occurrence of diseases in individual patients. This concept goes beyond the comorbidity definition, is not based on a central disease, and allows the assessment of the cumulative effect of chronic conditions [5]. Some recent studies have introduced comprehensive analyses including pairs, organ domains, or cumulative effects but there is still a need to deepen understanding of the additive impact of chronic conditions on disability and quality of life [26–29]. For example, McDaid et al (2013) recently presented a study assessing the effect of multiple chronic conditions on disability and quality of life in which the importance of co-occurring conditions was considered. One of its limitations was the classification of diseases into 4 groups (cardiovascular diseases, lung diseases, chronic pain, diabetes), so that the real impact of each condition was not assessed independently. Despite this limitation, it is one of the few papers assessing the effect of the number of chronic conditions on disability and quality of life [26]. Griffith et al (2010) also showed interesting results regarding chronic conditions taking multimorbidity into account. However, they opted to add pairs or triads of chronic conditions to the model rather than the number of chronic conditions [29].

Over recent years, the need to provide guidelines that consider the impact of co-occurring chronic conditions has been highlighted [25]. Thus, evaluation of the impact of multiple chronic conditions on quality of life and disability is essential as a first step to guide research and adjust guidelines, especially in Spain, where very little information is available [30,31]. The importance of detecting the leading preventable causes of negative health outcomes, such as disability, is central to facilitating responses at a public health level. Thus, quantifying the chronic disease burden is essential [32]. Moreover, variability in methodology in previous studies underlines the need to provide results using standardized tools that allow cross-national comparisons in the future. Furthermore, gender differences are known to exist with respect to disability, quality of life and chronic diseases but very little is known about the relationship between them [18,33,34]. Finally, since most of the studies referring to index conditions have been carried out in a clinical setting, a more comprehensive public health perspective is needed focusing especially on the elderly, the age group most frequently affected by multimorbidity.

Understanding the factors that interact with disability and quality of life is essential to find ways of assessing, preventing and dealing with these issues at a public health level. This paper aims to assess the individual, combined and cumulative impact of chronic physical and mental conditions on quality of life and disability in a representative sample of older adults in the Spanish general population. Secondly, the paper aims to provide evidence on these issues across gender.

Methods

Design

The COURAGE in Europe project is a cross-sectional household survey conducted on a representative sample of the non-institutionalized adult population in Finland, Poland and Spain [35]. Data from the Spanish sample is analyzed in the current paper.

Sample and procedures

A national representative sample of the Spanish adult population was selected by a stratified multistage clustered area probability method. A community-residing population over 18 years old was the target group. Three samples were chosen according to age: 18–49 years; 50–79 years; ≥80 years. Subgroups 50+ and 80+ years were oversampled, since these were the main target of the study. Exclusion criteria consisted of: lack of fluency in Spanish, house vacant/occupants elsewhere, deceased informant, individual not accessible [institutionalized/incarcerated/hospitalized), and the mentally unfit. Eligibility criteria were not met for 2,649 adults, with "occupants elsewhere/vacant house" the most common cause (74%). The survey protocol was translated from English into Spanish following WHO translation guidelines for assessment instruments [36]. Lay interviewers were trained on the survey before its administration. Quality assurance strategies were implemented during fieldwork [37]. The final response rate was 69.9%, corresponding to 4,583 adults over 18 years old. The response rate took into account the following issues: completed interview, partial interview, final refusal, inability to locate household or individual respondent, unsafe or dangerous area preventing the access to the interviewee and completed interviews not approved because of quality control problems. Of these, final refusal was the main cause of exclusion (80% of the overall excluded). Face-to-face structured interviews were conducted through Computer-Assisted Personal Interviewing (CAPI) at respondents' homes between July, 2011 and May, 2012. The interviewer judged whether the interviewee had cognitive problems at the beginning of the interview. This was a subjective judgment, which was indicated in case of clear memory problems

or severe mental disorders. If unsure, the interviewer could ask two questions to help with the decision: "*a) How would you best describe your memory at present? Is it very good, good, moderate, bad or very bad? b) Compared to 12 months ago, would you say your memory is now better, the same or worse than it was then?*". At this stage, respondents who answer "bad" or "very bad" to the first question and/or "worse" to the second question were used to consider the respondent had memory problems. Moreover, all proxy interviewees were evaluated by a supervisor to confirm this decision. In this case, a short version of the survey was administered to a proxy respondent. Data from proxy respondents was not analyzed because diagnosis of physical conditions and mental disorders was not performed in the proxy interviews. Thus, the final analysis consisted of 3,625 participants over 50 years old, once the 166 proxy respondents and the 792 participants younger than 50 years old had been removed.

Data collection

Sociodemographic information included gender, age, marital status, education level, employment status and urbanicity. With regard to chronic physical conditions, participants were asked about having received a life-time diagnosis and treatment within the previous 12 months for angina, arthritis, asthma, chronic obstructive pulmonary disease (COPD), diabetes, edentulism, hypertension and stroke. Treatment was assessed with the following question: "Did you receive medication or other treatment for this disease during the last 12 months?". Additionally, validated algorithms based on clinical symptoms were implemented to detect undiagnosed cases [38]. These algorithms come originally from the WHO's SAGE study and are in line with current clinical guidelines and reference publications [38–46]. When at least one of the two previous criteria was met, the respondent was considered to have one of the following conditions: arthritis, asthma, angina, stroke or chronic lung disease. Current cataract was assessed through self-reported medical diagnosis with co-occurring symptoms of cataract (visual problems associated with light sources and symptoms of blurred vision) to prevent the inclusion of respondents that had received corrective surgery. The symptoms were assessed, as in the WHO's SAGE study questionnaire, with the following questions: "*In the last 12 months have you experienced any of the following: a)… cloudy or blurry vision? b)… vision problems with light, such as glare from bright lights, or halos around lights?*" Hypertension, diabetes and edentulism did not have symptomatic algorithms since they are mostly asymptomatic conditions. Previous 12-months depression and anxiety were assessed with an adapted version of the World Health Organization Composite International Diagnostic Interview (CIDI), according to DSM-IV criteria [47]. For the assessment of functioning and disability we used the 12-item, validated version of the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) [48]. Results range from 0 (no disability) to 100 (maximum disability). Quality of life was assessed through a modified version of the World Health Organization Quality of Life instrument (WHOQOL) called WHOQOL-AGE that has been specially adapted for the elderly population. This short-version contains 13 out of 100 questions from the original version and has been validated in populations over 50 years old [49]. Results range from 0 (minimum quality of life) to 100 (maximum quality of life).

Statistical analysis

Unweighted frequencies, weighted proportions, means, confidence intervals and cross tabulations were applied for descriptive analysis. The Chi-square test was used to measure differences in prevalence of chronic diseases, number of conditions and sociodemographic variables across gender. T-test was used to assess differences in age, quality of life and disability across gender. T-test was also applied to evaluate differences in disability and quality of life for chronic conditions across gender.

To assess which pairs of conditions should be included in the analysis we took into account all 55 possible combinations from our 11 conditions. Frequency of disease pairs was computed. For those combinations with a co-occurrence higher than 1%, we calculated the multimorbidity coefficient as follows: real prevalence of the combination divided by the expected prevalence (expected prevalence = prevalence disease A x prevalence disease B) [50,51]. We then selected the 10 pairs with the highest coefficient score, obtaining a list with the most prevalent and comorbid pairs in our population. The use of the multimorbidity index to further restrict our selection was made according to recent evidence in the study of comorbidity and multimorbidity that highlights the underlying structure (shared risk factors risks and biological links) present in some of these associations, which have great interest at several levels (understanding of ethiopathology, disease prevention, disease management, healthcare costs) [46,52]. We fitted a linear regression model for every combination to test whether interactions were present with regard to the dependent variable: quality of life and disability. Those pairs with p value $<$ 0.2 were considered to interact and were selected for ulterior analysis.

Adjusted multiple linear regression was used to examine the association between physical conditions and quality of life in participants over 50 years old (n = 3,625). The model was adjusted for age, gender, educational level, marital status, urbanicity, all chronic conditions and those interactions with $p<0.2$: asthma with chronic obstructive lung disease (asthmaxCOPD); cataract with diabetes (cataractxdiabetes). This model was replicated using the number of chronic conditions rather than the individual variables to assess the additive effect in quality of life. Analogous procedures were applied to assess the association between chronic conditions and disability, considering the significant interactions for this outcome: depression with anxiety (depressionxanxiety) and cataract with diabetes (cataractxdiabetes).

Analogously, separate regressions were carried out for males and females to assess trends according to gender, as shown in the tables. To clarify the interpretation of these separate regressions by gender, additional statistical tests were performed: interactions between each chronic condition variable and gender were computed. Interactions were found in depression with respect to quality of life; and in diabetes, co-occurring cataract-diabetes, and the number of chronic conditions with respect to disability. The distinct impacts by gender have to be considered when interpreting the results of these diseases across gender.

Although beta-coefficients in the regressions can be considered a measure of effect size, we also computed the squared eta values with the aim of clarifying the meaning of our results. Squared eta is interpreted as the proportion of variance in the outcome explained by the variance in the independent variable. General recommendations for interpretation of squared eta results for ANOVA and GLM were followed: 0.01 small; 0.06 medium; 0.14 large. Depression, arthritis and the number of chronic conditions were considered to have large effect on outcomes. The other chronic condition variables produced moderate or small/moderate effect size values. Gender was considered to have moderate/small size effect.

The statistical analyses considered the complex nature of the sample design. Weights were used in analyses to adjust for differential probabilities of selection within households, and post-

stratification weights to match the samples to socio-demographic distributions. Analyses were performed with IBM SPSS statistics 19.

Ethics statement

The COURAGE study was approved by the Ethics Review Committee at Fundació Sant Joan de Déu, Barcelona, Spain and the Ethics Review Committee, La Princesa University Hospital, Madrid, Spain. Written informed consent was obtained from all participants. All investigators worked according to the principles expressed in the Declaration of Helsinki.

Results

Characteristics of participants

The study population consisted of 3,625 participants. A summary of sociodemographic data, chronic condition prevalence, disability results and quality of life score can be seen in Table 1. Prevalence of chronic conditions differs across gender except for hypertension, diabetes, asthma, stroke, edentulism and two of the co-occurring combinations assessed: asthma-COPD and cataract-diabetes. Women had higher rates of arthritis, depression, anxiety, cataracts and the combination depression-anxiety while men had higher prevalence of angina and COPD. 67.9% of the sample had at least one chronic condition. Gender differences were found with regard to the number of chronic conditions, with women having a greater number of chronic conditions ($p<0.001$). Women also had poorer results in quality of life and disability than men.

Impact of chronic conditions on quality of life and disability

A summary of the scores for quality of life and disability are presented for every condition and for the number of conditions in Table 2. Depression, anxiety and stroke are the conditions with the highest impact on quality of life and disability scores. Hypertension is the condition with the lowest impact on quality of life and disabitlity of the diseases assessed. The number of chronic conditions is related to worse quality of life and disability.

Impact of single chronic conditions and multiple chronic conditions on disability are presented in Tables 3 and 4. Analogous information is given for quality of life in Tables 5 and 6. At a global level, the linear regression showed that, individually, each chronic condition was related to poorer results in quality of life and higher rates of disability, except for hypertension, where no statistically significant difference was found (Tables 3 and 5). In the regressions, higher educational level and being married were also related with better outcomes in quality of life and disability.

Co-occurring diabetes and cataracts were found to be associated with higher disability (β: 9.76; 95% CI: 4.27, 15.25) and lower quality of life (β: −4.01; 95% CI: −8.06, 0.05) (table 3 and table 5).

Co-occurring asthma and COPD was associated with positive quality of life (β: 5.17; 95%CI: 1.50, 8.85). Co-occurring depression and anxiety showed lower disability but the result was not statistically significant (β: −6.54; 95CI: −15.96, 2.89).

Suffering from several chronic conditions was associated with higher disability, with scores in the questionnaire ranging from 3.6 (95% CI: 3.0, 4.1) to 38.2 (95% CI: 35.4, 40.9) when comparing people with no diseases and people with 1 and 4+ conditions respectively.

Similar changes were found with regard to the number of conditions and quality of life, where the score fell from 76.5 (95% CI: 75.6, 77.4) to 56.2 (95% CI: 53.5, 58.9). The regressions showed a strong association between the number of chronic conditions and both higher disability and worse quality of life (Table 4 and Table 6).

Gender trends in quality of life and disability

As for diseases considered independently, women had poorer results in disability scores compared with men with the same conditions, except for asthma, depression and anxiety where no difference was found (Table 2). Similar results were found in quality of life although, in this case, stroke also showed no difference across gender (Table 2). At an additive level, women also had worse outcomes when considering a specific number of chronic conditions, although having 4+ chronic conditions was related to similar outcomes.

With regard to the regressions results, anxiety and angina were only related to worse quality of life in women, while asthma and edentulism were associated with worse results only in men (table 5). For disability, separate regressions for men and women also showed particular trends. Anxiety, cataract and diabetes were only associated with poorer results for women while asthma was associated with poorer results only in men (table 3). An increasing positive association between the number of conditions and poor results in disability and quality of life was found for both sexes (table 4, table 6). Being single resulted in poorer results in quality of life compared with being married only in men (table 5).

Discussion

This study has shown that there is a strong association between chronic conditions and poor results in disability and quality of life, both at individual and additive level. Our study also showed relevant trends according to gender in this association.

Individual associations

The most remarkable result is that mental disorders (depression and anxiety) have a higher impact on quality of life and disability than most chronic physical conditions. Some studies have suggested an intimate association between mental disorders and changes in quality of life and disability in the elderly but they tend to focus specifically on mental conditions or combinations of mental disorders so that individual qualitative or quantitative comparisons between different mental and physical chronic diseases are not available [27,28,53–55]. Moreover, a high proportion of studies to date did not include mental disorders when analyzing chronic conditions [15,26,29,56]. There are few studies available which include mental and physical conditions, which show mixed results, so our results highlight the importance of mental health in the elderly at this level [10,57–59]. Stroke is the physical condition with the highest impact on quality of life, followed by COPD, arthritis and angina. These conditions share some similarities such as physical limitations or disabling symptoms (pain, shortness of breath, etc.), having been previously associated with poor health outcomes [26,60–65]. Asymptomatic conditions such as diabetes or edentulism resulted in a lower impact on quality of life. In this regard, our results complement the results of previous studies that found a mixed effect of diabetes on quality of life and disability but, in this study, we provide the additional context of other chronic conditions [31,34,56,59,66–68]. Hypertension turned out not to be associated with worse outcomes while earlier studies have shown mixed results [15,19,34,56,69–71]. When interpreting our results, it has to be considered that the hypertension diagnosis was reported by the respondents, so that a great proportion may have been receiving medical care at the time of the interview. It has been shown that

Table 1. Description of the sample of the Spanish Cohort of the COURAGE study.

	TOTAL	MALE	FEMALE	p value
Sample (n; %)	3625 (100%)	1643 (46.2%)	1982 (53.8%)	-
Age (mean, SE)	66.45 (0.18)	65.77 (0.27)	67.05 (0.24)	0.001
Education (n; %)				<0.001
no education	1207 (32.6%)	499 (29.7%)	708 (35.0%)	
primary	1075 (31.2%)	477 (30.2%)	598 (32.2%)	
secondary	949 (25.5%)	449 (27.2%)	500 (24%)	
university	393 (10.7%)	218 (12.9%)	175 (8.8%)	
Household income (n; %)				<0.001
1st quintil	686 (22.0%)	304 (20.8%)	382 (23.1%)	
2nd quintil	694 (21.7%)	254 (17.7%)	440 (28.2%)	
3rd quintil	715 (21.6%)	311 (20.9%)	404 (25.6%)	
4th quintil	745 (21.7%)	376 (25.0%)	369 (18.8%)	
5th quintil	428 (13.0%)	229 (15.6%)	199 (10.7%)	
Marital Status (n; %)				<0.001
single	310 (8.5%)	148 (9.0%)	162 (8.0%)	
married	2258 (62.1%)	1262 (77.5%)	996 (48.9%)	
divorced	266 (6.9%)	101 (5.4%)	165 (8.2%)	
widow	791 (22.5%)	132 (8.1%)	659 (34.9%)	
Urbanicity (n; %)				0.649
urban	3138 (83.8%)	1421 (84.3%)	1717 (83.4%)	
rural	487 (16.2%)	222 (15.7%)	265 (16.6%)	
Work (n; %)				<0.001
retired	1385 (41.3%)	884 (58.2%)	501 (26.9%)	
other	1269 (35.7%)	241 (14.9%)	1028 (53.5%)	
working	817 (23.0%)	435 (26.9%)	382 (19.6%)	
QoL score (mean, SE)	71.02 (0.36)	73.35 (0.39)	69.02 (0.46)	<0.001
Disability score (mean, SE)	13.18 (0.52)	9.30 (0.50)	16.51 (0.74)	<0.001
Hypertension (n; %)	1331 (37.3%)	568 (35.6%)	763 (38.9%)	0.051
Diabetes (n; %)	514 (14.0%)	255 (15.1%)	259 (13.1%)	0.078
Angina (n; %)	236 (6.6%)	128 (7.8%)	108 (5.7%)	0.047
Asthma (n; %)	231 (6.3%)	90 (5.4%)	141 (7.1%)	0.064
Arthritis (n; %)	982 (26.8%)	266 (15.8%)	716 (36.3%)	<0.001
COPD (n; %)	233 (6.7%)	124 (8.3%)	109 (5.4%)	0.002
Stroke (n; %)	132 (4.6%)	62 (5.0%)	70 (4.3%)	0.428
Depression (n; %)	434 (12.1%)	117 (6.7%)	317 (16.7%)	<0.001
Anxiety (n; %)	55 (1.4%)	13 (0.6%)	42 (2.0%)	<0.001
Cataracts (n; %)	215 (6.0%)	62 (4.6%)	153 (7.2%)	<0.001
Edentulism (n; %)	677 (18.8%)	295 (17.3%)	382 (20.2%)	0.052
Asthma_COPD (n; %)	103 (2.9%)	55 (3.3%)	48 (2.5%)	0.205
Depression_anxiety (n; %)	42 (1.1%)	9 (0.4%)	33 (1.6%)	<0.001
Caratact_diabetes (n; %)	65 (1.7%)	21 (1.3%)	44 (2.0%)	0.060
Num chronic conditions (n; %)				<0.001
0	1173 (32.1%)	594 (36.4%)	579 (28.3%)	
1	1074 (29.6%)	531 (31.3%)	543 (28.2%)	
2	688 (18.5%)	275 (16.3%)	413 (20.4%)	

Table 1. Cont.

	TOTAL	MALE	FEMALE	p value
3	372 (10.7%)	133 (9.1%)	239 (12.1%)	
4+	318 (9.1%)	110 (6.8%)	208 (11.0%)	

Unweighted frequencies, and weighted means and proportions are displayed. Chi-square test for 2xN tables and T-test were performed to compare across gender. NOTE: Household income was divided into 5 quintiles (the first indicating the lowest income). Education category 'no education' included those people that had never been to school or did not finish primary school. Marital status 'married' category included currently married or cohabiting. Employment 'other' category included training, homemakers, unemployed, voluntary work, health problems, caring for family, sick leave, no need to work, temporary time off and voluntary work. Anxiety included Generalized Anxiety Disorder and Panic Disorder. Abbreviations: SE, standard error.

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symptoms are responsible for the greatest impact on quality of life in patients with hypertension so that patient monitoring and treatment would minimize the few symptoms present in the participants with hypertension [72]. Efforts to improve quality of life and disability should focus on prioritizing mental disorders and physical symptomatic conditions.

Pair combinations

With regard to co-occurring pairs of conditions, suffering from diabetes and cataracts resulted in a synergic effect on disability and quality of life. These results must be treated with caution. Prevalence of cataracts is known to be strongly related to the duration of diabetes and parameters reflecting poor diabetes management, such as high levels of HbA1c, fasting blood sugar or macroalbuminuria [73,74]. This poor control of diabetes, which could also be related to other metabolic syndrome complications, would lead the individual to a poorer health status and higher degree of disability compared with the expected addition of the individual effects of diabetes and cataracts.

Co-occurrence of asthma and COPD resulted in contrary directionality of the results compared with the individual effect of the diseases on quality of life. It does not alter the individual negative effect of asthma and COPD on quality of life but suggests a ceiling effect when having them simultaneously. Both asthma and COPD are highly prevalent conditions in the elderly and this has been defined as the asthma-COPD overlap syndrome, which describes a frequency of overlapping diagnoses over 50% in COPD patients aged over 80 years [75]. As the name suggests, this situation involves features of both conditions and has recently been related to poorer quality of life than that found in asthma cases and similar to that of COPD [76]. In our case, 43% of the participants diagnosed with COPD also suffered from asthma, which supports the results seen in clinical settings. Some clinical outcomes, which may differ from the individual conditions, could be related to these results. For example, Fu et al. (2013) found, in a longitudinal study, that patients with asthma-COPD overlap had a better prognosis than COPD or asthma patients, although other studies have showed more severe exacerbations when these conditions co-occur [77,78]. Further research is needed to describe the asthma-COPD overlap and its impact on quality of life.

Co-occurring depression and anxiety resulted in lower effects on disability than theoretically expected although these results were not statistically significant. Further study is needed to clarify the combined impact of mental disorders in quality of life and disability due to the close relationship between these disorders.

Additive impact of chronic conditions

At an additive level, there is a sharp and continuous decrease in quality of life when suffering from more chronic conditions, with Beta ranging from −3.26 (95% CI: −4.66, −1.93) in the group of respondents with one chronic disease to −18.10 (95% CI: −20.95, −15.25) in the group with four and more conditions, which underlines the relevance of multimorbidity in this outcome. Similar results are found when assessing the association between multimorbidity and disability with Beta results ranging from 3.57 (95% CI: 2.56, 4.56) in respondents with one condition up to 27.64 (95% CI: 24.99, 30.29) in patients with four and more conditions. These results expand and complement the evidence since most studies have focused on the impact of individual conditions, specific pairs of conditions or organ domain classifications. [10,15,22,28,29,34,53,55,57,69,70,79,80]. Our results support the descriptive analysis made by Lawson et al. (2013) in which participants reporting longstanding conditions presented reductions in preference-weighted health-related quality of life. Their results, however, are not completely comparable since they counted up to three chronic diseases, considered different conditions and the count itself only allowed one condition for every organ-based classification group [81]. Brettschneider et al. (2013) and Heyworth et al. (2009) found that overall quality of life and its dimensions, measured with the EQ-5D, decreased with an increasing number of chronic diseases [59,82]. However, the study by Brettschneider et al. (2013) considered multimorbidity as a continuous variable without assessing the impact of the specific disease count, while Heyworth et al. (2009) only took six conditions into account, excluding mental health, so that results are complementary rather than comparable. On the other hand, Tan et al. (2013) also found poorer results in quality of life with a higher number of chronic conditions. However, there seemed to be a ceiling effect between two and three chronic conditions while, in our results, the group with four or more conditions shows a noticeably lower quality of life compared with respondents with three chronic conditions [71]. Our results in quality of life should help to target multimorbidity patients as population subgroups in which clinical, community and patient-centered care should be prioritized to ensure the best possible quality of life [83]. With regard to disability, little effort has previously been made in considering the additive effect of chronic conditions, as stated above. Our results suggest that multimorbidity patients require special attention due to the association between the number of chronic conditions and disability rates. Since disability per se predicts future disability status and is related to poor health outcomes, it is important to identify high-risk groups to develop preventive, curative or palliative strategies [34]. For example, patients at risk can benefit from interventions, such as resistance strength training or preventive home visitation programs [84].

Gender trends

It is known that systematic gender-dependent errors can be made when analyzing the results of a study due to androcentrism or gender insensitivity [85]. Previous research on these topics has

Table 2. Quality of life and disability scores in the sample, overall and by gender.

	Disability	Disability Male	Disability Female	p value	QoL	QoL male	QoL female	p value
Hypertension	17.8 (16.2–19.3)	12.3 (10.4–14.1)	22.1 (20.1–24.1)	<0.001	69.2 (68.1–70.2)	72.1 (70.8–73.5)	66.8 (65.4–68.3)	<0.001
Diabetes	21.4 (19.4–23.5)	15.2 (12.5–17.8)	27.7 (25.0–30.4)	<0.001	66.6 (65.1–68.0)	69.5 (67.3–71.7)	63.6 (61.8–65.5)	<0.001
Angina	28.4 (25.3–31.5)	21.1 (17.6–24.7)	36.9 (31.8–41.9)	<0.001	62.9 (60.9–65.0)	67.7 (65.0–70.3)	57.4 (53.8–61.0)	<0.001
Asthma	27.0 (24.1–30.0)	24.1 (19.8–28.4)	28.9 (25.3–32.6)	0.109	62.9 (61.0–64.8)	64.8 (62.4–67.1)	61.7 (59.0–64.5)	0.109
Arthritis	24.4 (22.5–26.4)	20.2 (17.7–22.8)	26.0 (23.4–28.6)	0.002	65.2 (63.9–66.4)	67.9 (65.8–70.0)	64.2 (62.6–65.7)	0.005
COPD	29.5 (25.6–33.3)	25.9 (21.1–30.8)	34.1 (29.4–38.8)	0.014	61.3 (58.5–64.2)	64.1 (60.5–67.8)	57.7 (54.3–61.1)	0.006
Stroke	30.5 (25.5–35.4)	27.0 (20.9–33.0)	34.0 (27.5–40.5)	0.044	60.9 (56.7–65.2)	65.2 (62.1–68.3)	56.6 (48.5–64.7)	0.065
Depression	33.0 (29.6–36.3)	30.0 (25.3–34.6)	34.0 (29.4–38.5)	0.257	54.6 (52.7–56.5)	53.6 (51.0–56.3)	54.9 (52.4–57.3)	0.509
Anxiety	33.2 (28.6–37.9)	29.8 (16.3–43.8)	34.2 (28.6–39.8)	0.578	50.7 (47.9–55.1)	57.4 (47.9–66.9)	48.9 (44.8–52.9)	0.075
Cataracts	29.7 (26.5–32.9)	23.4 (18.2–28.5)	33.2 (29.6–36.8)	0.002	62.4 (60.5–64.3)	65.4 (62.2–68.6)	60.8 (58.4–63.2)	0.031
Edentulism	22.1 (20.2–24.0)	16.4 (14.0–18.8)	26.3 (23.6–29.1)	<0.001	66.9 (65.1–68.8)	69.5 (67.7–71.3)	65.0 (62.1–67.9)	0.11
Asthma-COPD	32.9 (29.6–36.2)	30.7 (25.7–35.7)	35.4 (29.8–40.96)	0.250	60.1 (57.8–62.4)	62.3 (59.2–65.5)	57.6 (53.6–61.6)	0.078
Depression-anxiety	35.98 (30.8–41.2)	33.2 (18.1–48.3)	36.6 (31.0–42,3)	0.639	47.1 (43.3–51.0)	52.7 (42.6–62.8)	45.8 (41.5–50.1)	0.190
Caratact-diabetes	41.7 (36.7–46.8)	35.6 (26.0–45.3)	45.0 (39.6–50.5)	0.091	55.7 (52.5–59.0)	59.6 (52.4–66.9)	53.7 (50.5–56.8)	0.145
Num chronic conditions								
0	3.6 (3.0–4.1)	2.8 (2.2–3.4)	4.5 (3.6–5.3)	0.001	76.5 (75.6–77.4)	77.1 (76.1–78.0)	75.9 (74.7–77.0)	0.038
1	9.6 (8.5–10.7)	6.9 (6.1–7.8)	12.2 (9.9–14.4)	<0.001	72.6 (71.2–74.0)	74.6 (73.4–75.8)	70.7 (68.9–72.6)	<0.001
2	16.9 (15.4–18.4)	13.0 (10.5–15.5)	19.6 (17.9–21.3)	<0.001	70.2 (68.8–71.5)	72.8 (71.0–74.6)	68.3 (66.6–70.1)	<0.001
3	24.1 (22.0–26.2)	18.5 (15.1–21.9)	27.8 (24.9–30.6)	<0.001	64.3 (62.9–65.7)	66.0 (63.9–68.2)	63.2 (61.3–65.1)	0.061
4+	38.2 (35.4–40.9)	34.0 (29.1–38.8)	40.4 (37.1–43.7)	0.033	56.2 (53.5–58.9)	58.8 (55.9–61.7)	54.8 (51.0–58.6)	0.104

Weighted means of quality of life and disability results for people with each condition are displayed. Results are presented for the overall sample and by gender groups. Results with 95% Confidence interval. Statistical significance from gender comparison is showed (T-test analysis). NOTE: Abbreviations: QoL, quality of life.

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Table 3. Impact of chronic conditions on disability.

	Disability global		Disability male		Disability female	
	B (95% CI)	p value	B (95% CI)	p value	B (95% CI)	p value
Intercept	−11.75 (−17.76,−5.74)	<0.001	−5.18 (−11.34,0.97)	0.098	−14.68 (−22.30,−7.05)	<0.001
Sex (ref. male)	2.92 (1.72,4.12)	<0.001	-	-	-	-
Age (per each additional year)	0.32 (0.24,0.41)	<0.001	0.22 (0.12,0.31)	<0.001	0.42 (0.31,0.53)	<0.001
Marital status (ref: married)						
divorced/separated	−0.55 (−2.70,1.59)	0.609	1.46 (−0.82,3.76)	0.207	−1.50 (−4.23,2.23)	0.28
widow	2.15 (0.60,3.70)	0.007	1.66 (−0.94,4.26)	0.208	1.36 (−0.69,3.41)	0.192
single	0.61 (−1.11,2.33)	0.486	−0.13 (−1.91,1.65)	0.886	0.83 (−2.14,3.81)	0.582
Education level (ref: no studies)						
primary	−3.89 (−5.46/−2.320)	<0.001	−3.85 (−5.64,−2.06)	<0.001	−3.81 (−6.24,−1.38)	0.002
secondary	−4.62 (−6.23,−3.02)	<0.001	−5.15 (−7.05,−3.25)	<0.001	−4.09 (−6.17,−2.00)	<0.001
university	−5.80 (−7.99,−3.62)	<0.001	−4.92 (−6.69,−3.16)	<0.001	−6.78 (−10.16,−3.40)	<0.001
Urbanicity (ref: rural)	−3.17 (−5.07,−1.27)	0.001	−2.61 (−5.04,−0.19)	0.034	−3.58 (−6.13,−1.03)	0.006
Chronic conditions						
depression	15.70 (13.62,17.77)	<0.001	16.14 (12.10,20.17)	<0.001	15.60 (13.14,18.06)	<0.001
anxiety	11.17 (2.49,19.86)	0.012	11.40 (−11.52,34.32)	0.327	11.94 (1.32,22.56)	0.028
angina	6.87 (4.52,9.22)	<0.001	6.01 (3.31,8.71)	0.034	7.62 (3.55,11.70)	<0.001
asthma	2.34 (0.28,4.40)	0.03	4.00 (0.17,7.83)	0.041	1.42 (−1.35,4.20)	0.311
COPD	8.63 (6.21,11.05)	<0.001	9.12 (5.44,12.80)	<0.001	8.32 (4.84,11.80)	<0.001
cataract	3.28 (0.37,6.19)	0.027	0.08 (−4.82,4.97)	0.975	4.60 (1.01,8.18)	0.012
arthritis	7.50 (5.95,9.06)	<0.001	7.41 (4.92,9.90)	<0.001	7.38 (5.42,9.34)	<0.001
diabetes	2.32 (0.56,4.08)	0.010	0.79 (−0.95,2.53)	0.373	4.25 (1.57,6.94)	0.002
hypertension	0.14 (−0.97,1.25)	0.802	−0.37 (−1.60,0.86)	0.554	0.170 (−1.65,1.99)	0.854
edentulism	2.93 (1.19,4.68)	0.001	3.08 (1.00,5.16)	0.004	2.79 (0.03,5.54)	0.048
stroke	12.15 (8.08,16.22)	<0.001	15.90 (9.66,22.14)	<0.001	9.17 (4.13,14.21)	<0.001
Interactions						
depression-anxiety	−6.54 (−15.96,2.89)	0.172	−2.59 (−28.70,23.52)	0.845	−8.04 (−19.52,3.43)	0.168
caratact-diabetes	9.76 (4.27,15.25)	0.001	15.41 (5.99,24.84)	0.002	6.28 (−0.59,13.15)	0.073

Linear regression model for the global sample was adjusted for sex, age, marital status, education level, urbanicity, individual chronic conditions and interactions. Analogous linear regressions were performed for male and female, adjusted by the same variables but sex. Results with 95% Confidence interval.
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highlighted the specific need to address disparities and differences in risk and interventions across gender groups of people with chronic conditions [83]. Studies tend to consider gender when adjusting the regression models but only some of them provide descriptive results or separate analyses by gender, which in turn are usually focused on specific conditions [10,29,33,63,68,86–88]. Consequently, our results covered the global sample as well as those for males and females.

Our results have shown that women had higher risk of disability than men after adjusting for covariates (β: 2.92; 95% CI: 1.72, 4.12) although the clinical relevance of this result is unclear since there are no clinical cut-offs for these types of screening tools

Table 4. Impact of multiple chronic conditions on disability.

Number of chronic conditions (ref: not having a condition)	Disability global		Disability male		Disability female	
	B (95% CI)	p value	B (95% CI)	p value	B (95% CI)	p value
1	3.57 (2.56,4.56)	<0.001	2.80 (1.66,4.85)	<0.001	4.40 (2.67,6.13)	<0.001
2	8.59 (6.92,10.27)	<0.001	7.32 (5.14,9.49)	<0.001	9.90 (7.54,12.26)	<0.001
3	14.61 (12.54,16.69)	<0.001	13.40 (10.06,16.74)	<0.001	15.59 (12.69,18.48)	<0.001
4+	27.64 (24.99,30.29)	<0.001	27.11 (2.38,22.40)	<0.001	28.23 (24.82,31.63)	<0.001

Linear regression model for the global sample was adjusted for sex, age, marital status, education level, urbanicity and number of chronic conditions. Analogous linear regressions were performed for male and female, adjusted by the same variables but sex. Results with 95% Confidence interval.
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Table 5. Impact of chronic conditions on quality of life.

	QoL global		QoL male		QoL female	
	B (95% CI)	p value	B (95% CI)	p value	B (95% CI)	p value
Intercept	72.80 (69.41,76.19)	<0.001	72.89 (67.89,77.88)	<0.001	73,79 (68.65,78.93)	<0.001
Sex (ref. male)	−0.91 (−1.81,−0.01)	0.048	-	-	-	-
Age (per each additional year)	0.04 (−0.02,0.09)	0.166	0.05 (−0.02,0.11)	0.197	−0.01 (−0.08,0.07)	0,918
Marital status (ref: married)						
divorced,separated	−6.63 (−8.48,−4.77)	<0.001	−8.82 (−11.98,−5.67)	<0.001	−5.07 (−7.37,−2.76)	<0.001
widow	−2.73 (−4.05,−1.42)	<0.001	−3.39 (−5.62,−1.15)	0.003	−1.71 (−3.30,−0.12)	0.035
single	−3.47 (−5.43,−1.52)	0.001	−5.55 (−8.15,−2.95)	<0.001	−0.83 (−3.70,2.03)	0.566
Education level (ref: no studies)						
primary	2.76 (1.40,4.12)	<0.001	2.43 (0.55,4.30)	0.011	2.93 (1.16,4.70)	0.001
secondary	5.08 (3.32,6.82)	<0.001	4.48 (2.44,6.52)	<0.001	5.36 (3.01,7.72)	<0.001
university	7.75 (6.02,9.47)	<0.001	6.51 (4.27,8.75)	<0.001	8.34 (5.87,10.85)	<0.001
Urbanicity (ref: rural)	−0.96 (−2.70,0.79)	0.279	−0.78 (−2.77,1.22)	0.443	−1.49 (−3.65,0.673)	0.176
Chronic conditions						
depression	−14.00 (−15.85,−12.14)	<0.001	−17.00 (−19.98,−14.03)	<0.001	−12.79 (−15.15,−10.44)	<0.001
anxiety	−7.82 (−11.57,−4.08)	<0.001	−3.60 (−9.40,−2.19)	0.221	−9.29 (−13.77,−4.80)	<0.001
angina	−3.45 (−5.20,−1.69)	<0.001	−2.30 (−4.71,0.10)	0.060	−4.67 (−7.55,−1.78)	0.002
asthma	−3.40 (−5.49,−1.32)	0.002	−4.66 (−7.05,−2.26)	<0.001	−2.57 (−5.40,0.26)	0.075
COPD	−6.19 (−8.39,−4.00)	<0.001	−5.33 (−8.61,−2.05)	0.002	−7.00 (−10.51,−3.49)	<0.001
cataract	−2.49 (−4.61,−0.37)	0.022	−2.58 (−5.56,0.40)	0.089	−2.35 (−5.08,0.38)	0.091
arthritis	−3.52 (−4.65,−2.38)	<0.001	−3.52 (−5.31,−1.73)	<0.001	−3.45 (−4.83,−2.07)	<0.001
diabetes	−1.49 (−2.87,−0.11)	0.035	−1.60 (−3.29,0.10)	0.065	−1.21 (−3.24,0.82)	0.241
hypertension	0.38 (−0.50,1.26)	0.397	0.538 (−0.69,1.77)	0.389	0.45 (−0.88,1.77)	0.505
edentulism	−1.63 (−3.01,−0.26)	0.020	−2–21 (−3.85,−0.58)	0.008	−1.08 (−3.23,1.07)	0.322
stroke	−8.16 (−11.77,−4.55)	<0.001	−7.93 (−11.47,−4.38)	<0.001	−8.88 (−15.34,−2.42)	0.007
Interactions						
asthma-COPD	5.17 (1.50,8.85)	0.006	5.44 (0.41,10.48)	0.034	5.80 (−0.74,12.33)	0.082
caratact-diabetes	−4.01 (−8.06,0.05)	0.053	−4.64 (−13.10,3.83)	0.281	−3.87 (−8.71,0.97)	0.116

Linear regression model for the global sample was adjusted for sex, age, marital status, education level, urbanicity, individual chronic conditions and interactions. Analogous linear regressions were performed for male and female, adjusted by the same variables but sex. Results with 95% Confidence interval.
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(effect size resulted in moderate-small values). This result is comparable with the effect of diseases, such as diabetes (β: 2.32; 95% CI: 0.56, 4.08), but very low compared with depression (β: 15.70; 95% CI: 13.62, −17.77) or stroke (β: 12.15; 95% CI: 8.08, −16.22). Analogous results were found for quality of life.

Our results show higher disability and lower quality of life average scores in women than in men for most chronic conditions (e.g. women with angina had considerably higher scores for disability and lower for quality of life compared with men). These results reinforce the general idea that greater attention should be paid to women to prevent and manage poor outcomes in disability

Table 6. Impact of multiple chronic conditions on quality of life.

Number of chronic conditions (ref: not having a condition)	QoL global		QoL male		QoL female	
	B (95% CI)	p value	B (95% CI)	p value	B (95% CI)	p value
1	−3.29 (−4.66,−1.93)	<0.001	−1.98 (−3.37,−0.60)	0.005	−4.68 (−6.73,−2.62)	<0.001
2	−5.15 (−6.62,−3.69)	<0.001	−3.89 (−5.74,−2.04)	<0.001	−6.15 (−8.15,−4.14)	<0.001
3	−10.67 (−12.34,−9.00)	<0.001	−11.01 (−13.42,−8.60)	<0.001	−10.70 (−12.93,−8.48)	<0.001
4+	−18.10 (−20.95,−15.25)	<0.001	−16.85 (−19.93,−13.77)	<0.001	−19.04 (−23.19,−14.88)	<0.001

Linear regression model for the global sample was adjusted for sex, age, marital status, education level, urbanicity and number of chronic conditions. Analogous linear regressions were performed for male and female, adjusted by the same variables but sex. NOTE: QoL = quality of life. Results with 95% Confidence interval.
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and quality of life. Additionally, it specifically clarifies this topic with regard to chronic conditions [68,89–91]. However, similar quality of life and disability scores were found in both sexes for depression, anxiety, asthma and stroke (only for quality of life in stroke). When comparing the global scores across gender, a greater impact is seen in women but this difference disappears with respect to quality of life when three or more conditions are present. The impact of the increasing number of chronic conditions would appear to be similar across gender when people reach a certain level of multimorbidity.

When assessing the regression models for males and females, most conditions showed similar behavior as the reported in the regression including all participants. For some conditions, however, this association disappeared in men or women. Anxiety and angina were statistically related to poorer results in women only, while asthma and edentulism were related to poorer results solely in men. Since anxiety prevalence in men was relatively low, we think this result may be biased by the power of the study. Analogously, anxiety, cataracts and diabetes were associated with higher rates of disability solely in women while asthma was found to be related to higher disability in men. With regard to the number of chronic conditions, a greater impact on quality of life and disability was found in both genders. These results suggest that the effect of conditions in each gender group may differ and should be considered in future studies. With regard to asthma, for example, the management of the disease in men should focus particularly on preventing loss of quality of life and physical functioning.

Strengths and limitations

Our study's main strength is that results are extrapolated to the entire Spanish older adult population. In the future, comparison will be possible with other countries included in the COURAGE and SAGE studies. It is also remarkable that the selection of chronic diseases, including depression and anxiety, were mainly omitted in previous studies despite having been related to poor health outcomes at an individual level. Diagnosis by means of both self-report plus symptom algorithms also allows a more complete picture of the participants to emerge compared with other studies. There are, however, limitations in our study. Its cross-sectional nature identifies associations but does not allow conclusions on cause-and-effect relationships to be drawn. Moreover, age effects may not be distinguished from cohort effects. Longitudinal studies are needed to better establish the association between multimorbidity, quality of life and disability, thus reducing this bias. Multimorbidity studies would benefit from a standardized definition and disease inclusion criteria [50]. For example, the exhaustive "Expanded Diagnosis Clusters of the ACG" system have been used in some studies, although it becomes complex to employ outside the clinical setting and in the case of poor integration of health care levels [92]. The choice of chronic conditions is also relevant since it is known that a higher number of assessed conditions results in a higher proportion of multimorbidity [5]. Our selection of chronic conditions was made according to the SAGE study, focusing on a limited number of highly prevalent conditions that are a major cause of disability, through a method that can be applied across countries. There is, however, a need to include diagnoses of other common conditions known to have a considerable impact on quality of life, disability and health care resources, in future studies. Research on multimorbidity, as highlighted by the recent review by Prados-Torres et et al. (2012), may include diseases such as malignancies, congestive heart failure or anemia [92].Moreover, when assessing specific pairs, we chose those highly prevalent pairs of conditions with a high degree of interaction shown in the multimorbidity index. However, further studies including other combinations are required to deepen knowledge of less common co-occurring conditions. The self-reported data-collection method could also bias the results, but this effect may be minimized as a good correlation between medical records and self-reported diagnosis has been found [93,94]. Our analysis does not allow consideration of the progression and severity of conditions, which would be advisable in future studies. For example, severe COPD cases or poor glycemic control in diabetes may be related to poorer health outcomes [95]. There is a possibility that some respondents who did not take the medication prescribed by their doctors answered that they were not receiving treatment and were incorrectly classified as "not suffering from a specific disease". This limitation is minimized since the question was quite open "did you received treatment", rather than asking whether they were "taking the medication" and also due to the inclusion of the symptoms algorithm in most conditions. With regard to the analyses including the number of chronic conditions, further study is needed to clarify if greater contribution to the results is due to some conditions rather than others. We considered theoretical similar impact in our analyses to be consistent with the previous literature on that regard. Another limitation when analyzing the results is the geopolitical context. Specific results for an individual condition may vary according to external factors that should be analyzed if detected [96,97]. Although financial crises may impact some results, such as the prevalence of mental disorders, recent evidence suggests that health in Spain has continued to improve during the first four years of the current economic recession, so it seems this bias would be reduced [98,99]. Finally, separate results for women and men (average scores and regression models) obtained in our article have shed some light on gender issues but further efforts focusing on differences across gender would be needed in future studies.

Conclusion

The results of this study contribute to a deeper understanding of the effect of chronic conditions on quality of life and disability. In Spain, multimorbidity is a prevalent phenomenon among elderly people in the community that increasingly affects both disability and quality of life as more co-occurring conditions accumulate. Multimorbidity patients should be considered as targets for clinical, community and patient-centered care based on preventive, curative or palliative strategies. Our results are especially relevant since little effort has been previously made to consider the additive effect of common chronic conditions on quality of life and disability. At an individual level, efforts to improve quality of life and disability should prioritize prevention and management of mental disorders and physical symptomatic conditions since they are associated with poorer outcomes than mainly asymptomatic conditions such as hypertension. Our results also highlight the need to include mental disorders, selected in very few previous studies, when analyzing multimorbidity because of their great impact on the results. Finally, there is need to consider gender as an important factor when assessing multimorbidity and designing interventions for multimorbidity patients since specific trends arise in some outcomes with women showing worse health results in most cases.

Author Contributions

Conceived and designed the experiments: JMH JLA MM BO. Performed the experiments: NG JMH JLA MM MVM BO. Analyzed the data: NG MVM BO MM JMH. Contributed reagents/materials/analysis tools: NG BO MVM JMH. Wrote the paper: NG AL BO JMH MM JLA. Critically revised the paper and approved the final version to be published: NG BO MVM AL JMH MM JLA.

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Chapter 4
General discussion

4.1. Multimorbidity patterns

4.1.1. Multimorbidity prevalence in Spain

Multimorbidity, defined as the co-occurrence of 2 or more chronic conditions, was present in 20% of the overall Spanish adult population. These results are consistent with other similar studies ranging from 20 to 30% in the general adult population [57,152,153]. Although most of the evidence available to date has tended to present data on very old subjects, our results highlight the importance of chronic conditions in relatively younger subgroups of adults, especially between 50-64 years old. For instance, more than a quarter of women between 50-64 years old suffered from multimorbidity. Future studies using a broader framework or focusing on middle-aged adults could lead to a deeper understanding of the course of chronic conditions and may lead to measures to prevent or better manage older multimorbidity patients.

Multimorbidity is known to increase with age. In Spain, we found that multimorbidity prevalence reached 67.3% and 52.9% in women and men over 65 years, respectively. These epidemic results are comparable to others found in recent publications [31,154]. An association with gender was also found, with women suffering from more physical, mental and overall conditions than men. These results are consistent with most multimorbidity studies, as shown in the review by Marengoni et al [31]. When examined individually, depression, cataracts and arthritis showed statistically significant differences across gender, with women suffering from higher rates (NOTE: “depression” refers to “last-12 month major depression”). These results show that special attention should be paid to the management of elderly women in health care as they are more prone to developing multimorbidity. This effect should be given special consideration as the impact on quality of life in women may be more severe than in men [155].

The assessment of individual prevalence of chronic physical conditions showed that hypertension, arthritis and cataracts were the most prevalent physical conditions in older adults, affecting over 40% in the 65+ subgroup. These results are similar to those found by the Spanish National Health Survey, where arthritis, hypertension and cataracts were the first, second and fifth most prevalent conditions [20]. In the case of cataracts, as they can be operated on, life-time prevalence would be higher and more similar to our result. The high prevalence of cardiovascular-related conditions should be highlighted as they are the second cause of premature mortality in Spain after cancer [156]. Edentulism was present in 24.9% of men and 31% of women over 65 years. This value is relevant because edentulism is not only

related to poorer quality of life but is also an indicator of the adequacy of the national oral health care system [157,158]. Our results support the importance given to the prevention and management of edentulism in a recent review by Emami et al as it can potentially lead to psychological, physical and social disability [159]. Chronic lung disease and asthma also showed significant increases across age. There is controversy regarding the prevalence of asthma in the elderly. It is assumed that asthma prevalence may decrease with age but some studies suggest underdiagnosis due to diagnostic difficulties [160,161]. However, our results are consistent with the last Spanish National Health Survey that showed the highest prevalence of asthma in the population over 85 years [20]. In fact, an "asthma-COPD overlap syndrome" has been defined in the elderly and patients with this syndrome may have components of both diseases [162]. Caution is advised when interpreting this outcome, since the overlapping symptoms between late onset asthma and chronic obstructive pulmonary disease could be present in our results. Since most of the physical conditions assessed in our study can be partially prevented (e.g., diabetes, chronic lung disease, angina), further efforts must be made in Spain to develop appropriate national health policies. Once established, tight control of some of these conditions is associated with better health outcomes, as are the case of glycemia control and the decrease of diabetes-associated complications. Thus, it is essential to optimize their management, which is especially important due to the high prevalence of conditions such as diabetes or hypertension.

Interesting results arise when comparing the prevalence of mental conditions across age and gender. No difference was found in the prevalence of anxiety when comparing age groups or gender groups despite the fact that women and the younger population were supposed to suffer from higher rates according to previous studies [163] (NOTE: "anxiety" includes generalized anxiety disorder and panic disorder). However, the prevalence of depression did show differences across age groups. The subgroups with the highest prevalence of depression were women aged 65+ (18%) and women 50-64 years (15.7%). Differences were also found across gender, with men suffering from lower rates of depression. For example, men over 65 and men aged 18-49 years only had 5.2% and 5.1% of major depression diagnosis respectively, which corroborates similar trends found in previous studies [164–166]. There is controversy surrounding the prevalence of mental disorders in the elderly. The ESEMeD study found a decrease in the prevalence of 12-month anxiety and mood disorders across age [163]. The sub-analysis in the Spanish sample showed similar results [167]. In the study, prevalence of any mental disorder in the last 12 months was lower than in our case; 9.8% in the 50–64 years group and 5.8% in the 65+ group. By contrast, some studies have shown a much higher

prevalence [168,169]. Differences among studies may be due to various factors. First, it has been pointed out that the elderly have to cope with cognitive decline, sensory impairment, fewer social relationships, cessation of activity and change of status, which could be related to variations in the incidence of mental disorders [170]. Second, there may be a large subgroup of patients with late-onset depression, present in patients with neurological abnormalities [166]. Moreover, economic recession is also a factor related to the current higher prevalence of mental disorders in Spain [171]. On the other hand, differences in prevalence may be partially explained by the diagnosis scheme selected in each study. Diagnostic interviews involving excessive cognitive requirements, and attribution of symptoms to physical illnesses, may affect the results in most studies leading to a lower prevalence of depression in the elderly [172]. New tools, such a specific version of the CIDI questionnaire for the population over 65, are currently being prepared to address this problem [173].

4.1.2. Multimorbidity patterns in the Spanish population

The results of our analysis revealed three multimorbidity patterns in the Spanish population aged 50 years and over, which is an especially relevant result considering the high rates of multimorbidity found in this population group. These patterns were: 1) "cardio-respiratory"; 2) "mental-arthritis"; and 3) "aggregate pattern". Additionally, some associations between chronic physical conditions and mental disorders were detected. These associations, both at an individual and cumulative level, are also notable as they could lead to better understanding and management of these conditions.

The first multimorbidity pattern, "cardio-respiratory", included angina, chronic lung disease and asthma. Prados-Torres et al in Spain and Newcomer et al in United States also found patterns which included pulmonary and cardiac conditions [37,174]. However, in those cases the patterns were more complex and included a wide range of other diseases, being classified as "cardiovascular/metabolic" or "mental health" patterns respectively, according to the review by Prados-Torres et al [47]. The association between pulmonary and cardiac diseases has been highlighted in a systematic review by Müllerova et al, where an increased risk of cardiovascular disease was found in COPD patients [175]. In fact, the presence of obstruction, restriction and respiratory symptoms have been found to be related to a higher risk of cardiovascular disease, even after adjusting for other conditions [176]. For instance, it has been found that Forced Expiratory Volume in 1 second (FEV1) is a predictor of cardiovascular risk after adjusting for other cardiovascular risk factors such as age, gender, tobacco consumption, education or cholesterol [177]. Smoking is also a common risk factor

in these diseases. Moreover, the association between cardiovascular and chronic pulmonary diseases may involve hypoxia, inflammation, oxidative stress or aging [176,177]. Atherosclerosis is closely connected to lipid metabolism but also to inflammation in all stages of the disease, with the involvement of leukocytes, macrophages and inflammatory mediators such as tumor necrosis factor or ɣ-interferon [178]. In COPD there is a pro-inflammatory systemic state which may exacerbate the atherosclerotic process and its consequent negative cardiovascular effects. Some authors have studied the cardiovascular effects of inhaled corticoids for COPD patients and have found mixed results, indicating that more evidence is needed [179–181]. With regard to healthcare utilization, the Lung Health Study found that 42% of hospitalizations of COPD patients were due to cardiovascular causes [177]. The study also reported that only 14% of the hospitalizations were due to respiratory causes. At the diagnostic level, the common symptoms shared by the conditions in this pattern should be highlighted. Shortness of breath or chest pain may overlap when suffering from these conditions simultaneously, which may also be relevant to the management of patients affected by these conditions.

The second multimorbidity pattern, “mental-arthritis”, includes depression, anxiety and arthritis. There has been growing interest and concern regarding the high rates of psychiatric comorbidity over recent years. Kessler et al found that more than half of all lifetime mental disorders tend to be concentrated in one sixth of the population who had a history of three or more comorbid psychiatric disorders, including depression and anxiety disorders [182]. Anxiety and depressive disorders are known to be comorbid in many cases. Results from The National Comorbidity Survey Replication (NCS-R) study, carried out in the United States, showed statistically significant associations between major depressive episode and all type of anxiety disorders [183]. The Netherlands Study of Depression and Anxiety (NESDA) found that 67% of patients with depressive disorders had a current anxiety disorder, and 75% a lifetime anxiety disorder. In turn, 63% of patients with a current anxiety disorder had a current depressive disorder and 81% had a lifetime depressive disorder [184]. Additionally, in the ESEMeD study, suffering from any type of anxiety disorder, such as generalized anxiety disorder or panic disorder, was clearly associated with a higher risk of major depression [185]. Anxiety and depression comorbidity has been shown to be related to more negative impact compared with the independent presence of these conditions. For example, suicidal ideation has been found to be strongly associated with comorbid depression and anxiety [186,187]. Thus, close attention should be paid to the management of patients affected by this comorbidity. The “mental-arthritis” pattern also linked arthritis to these psychiatric disorders;

although the association was less strong (factor score for arthritis was 0.27 in the pattern). This outcome supports the results found in the World Mental Health Surveys across 17 countries where arthritis indicated a higher risk of developing mood and anxiety disorders [188]. Moreover, comorbid depression-anxiety was found to be more strongly associated with arthritis than single mental disorders, which also supports our results [189]. Even though the specific mechanism underlying this relationship still remains unclear, longitudinal data suggest that arthritis would predict the onset of psychiatric disorders [190]. In addition, there is some evidence showing higher levels of IL-17, typically higher in patients with arthritis, in those patients with anxiety compared with those without [191]. Both osteoarthritis and rheumatoid arthritis are associated with greater pain intensity when patients are suffering from comorbid depression or anxiety [192,193]. In fact, patients with rheumatoid arthritis, knee osteoarthritis and fibromyalgia syndrome who also suffer from depression and/or anxiety have significantly lower quality of life compared with patients without these mental disorders [194]. Other factors, such as the impact of arthritis on the physical appearance and the presence of periods with remission of the clinical symptoms of arthritis are also thought to be involved in the association between these conditions [195,196]. Despite the need for further investigation, our results show that social support and a multidisciplinary approach to treating psychological distress in arthritis alongside conventional treatment are essential to manage comorbid arthritis and mental disorders [196–198]. Thus, mental screening should be performed in patients with arthritis in order to offer the most efficient care for these patients. Murphy et al (2012) previously encouraged health care providers to screen all people with arthritis for both anxiety and depression [199]. Selected patients could benefit from specific strategies aiming to improve their quality of life. For example, exercise, behavioral therapy and meditation have been proposed as ways of helping patients to manage the psychological burden associated with arthritis [197].

The third multimorbidity pattern is the broadest, including seven physical conditions: hypertension, diabetes, cataracts, stroke, edentulism, angina and arthritis. Because of the higher number of conditions and the lack of a clear, single framework, it was artificially named the “aggregate pattern”. Angina, hypertension, diabetes and stroke are related to each other through the metabolic syndrome. Some previous studies assessing multimorbidity patterns have only found specific patterns for conditions under this umbrella concept. For example, García-Olmos et al found a pattern involving cardiac arrhythmia, lipid metabolism disorders, hypertension and type 2 diabetes in Spain [57]. Similar patterns have been found by other authors in the United States and Germany [47,50]. Occasionally, as in our case,

multimorbidity patterns in the literature included typical metabolic syndrome conditions plus other non-metabolic conditions. In fact, Freund et al found a pattern with cardiovascular and metabolic diseases that also included osteoarthritis and visual impairment, which is very similar to the findings in our study [200]. Holden et al published a pattern with cardiometabolic diseases but also included arthritis [201]. In the review by Prados-Torres et al, patterns in which all or most conditions were related to cardiovascular and metabolic diseases were among the top three groups of multimorbidity patterns with relevant similarities [47]. With regard to the associations of diseases themselves, cataracts may be involved in this pattern as its prevalence is influenced by the presence of diabetes, but also bearing in mind that cataracts has been linked to joint diseases [50,202]. The underlying mechanisms that may exist between joint diseases and cataracts are unclear. Adverse effects of glucocorticoids for the treatment of rheumatism could be partially responsible for the higher prevalence of cataracts in these patients. However, Falsarella et al found a higher risk of developing cataracts after adjusting for glucocorticoid intake in patients with arthritis [203]. Thus, it has been suggested that an increase in inflammatory modulators in rheumatic disorders may also be related to the onset of cataracts [203]. For example, arthritis-related uveitis has been associated with the onset of cataracts due to both inflammation and intake of glucocorticoids [204]. Heart diseases have also been associated with joint diseases, which supports this pattern, and may be linked through inflammatory pathways [37,50]. A systematic review by Felton et al found a relationship between the presence of edentulism with hypertension, coronary artery disease, diabetes, rheumatoid arthritis and osteoporosis [205]. It has been suggested that edentulism may be related to arthritis through an inflammatory pathway and with cardiovascular diseases through dietary or inflammatory causes [205]. On the one hand there may be a lower intake of fruits, vegetables and fiber and increased consumption of cholesterol and saturated fats, which may be related to obesity, hyperlipidemia and lack of some antioxidants in the diet [159]. On the other hand, it has been suggested that increased inflammation rates cause changes of the gastric mucosa, gastrointestinal cancer and higher rates of ulcers [159].

4.1.3. Methodological issues in multimorbidity pattern analysis

As stated before, although the study of pair associations (comorbidity) is useful and has helped to improve medical practice in the past, there is also a need to study the additive association of multiple chronic conditions. Apart from the mere counting of diseases, which can be a good starting for work on chronic conditions, other more complex statistical techniques have been used in the past to assess multimorbidity patterns in the population. In

our case, we used factor analysis to detect multimorbidity patterns, although other methodologies have been employed in other studies. The systematic review by Prados et al, focusing on multimorbidity patterns, showed an updated list of studies in that respect. Only 14 studies were found focusing on multimorbidity patterns. When considering the statistical approach in the literature, we find 4 approaches, including the one followed in our study:

- Ratio observed/expected: This methodology has been used to assess whether certain pairs, triads or patterns of chronic conditions are more frequent in real life than theoretically expected. However, we cannot discount the possibility that the associations occur by chance as adjusted statistical analyses are not performed. For example, Freund et al compared the expected and observed prevalence by means of the Chi-Square test to assess multimorbidity patterns in Germany [200]. Since controlling for sex and age was not possible, Wong et al stratified for these variables to get a broader picture although doing this risks reducing the sample size excessively [44]. Thus, large databases are required to ensure the capacity to discriminate the patterns clearly. Although a more complex analysis would be desirable, this method allows a broader picture of multimorbidity distribution to emerge using a relatively easy, clear methodology. In our case, although it is not useful when exploring multimorbidity patterns, we used this approach to detect the pairs of conditions with higher observed/expected ratio to assess their impact on quality of life and disability, which will be commented on later in the discussion.

- Cluster analysis: this method allows individuals to be assigned to groups, called clusters, so that individuals within a group have similarities between them in terms of variables of interest. In other words, it divides data into groups that retain the natural structure of the data. Despite the statistical differences, the aim is the same as in multiple correspondence analysis and factor analysis. There have been a few instances of cluster analysis methodology being used for multimorbidity, by means of several techniques, especially agglomerative hierarchical clustering [45,51–53,174,206]. The main inconvenience of this approach is that conditions can be assigned to a single pattern only, which interferes with the natural conception of multimorbidity patterns. Moreover, when interpreting the typical cluster analysis dendrograms, the false impression can be created that all the data are distributed into groups, which, in fact, is a possibility that cannot be discounted in our case. Choosing the right number of clusters may be another problem since as the fusion process is performed, dissimilar clusters can become combined.

- Multiple correspondence analysis: This is a method with exploratory purposes that also reduces the dataset and shows its underlying structure. After performing the analyses, theoretical dimensions are reduced and the variables used in the analyses (in our case: chronic conditions, etc) are assessed by means of plots to detect associations (patterns in our case). This provides a representation of the datasets as clouds of points in a multidimensional Euclidean space [207]. There are some limitations when using this method. First, a number of decisions have to be made which can affect the final outcomes and allow some subjectivity to have an effect on the results. According to Glynn et al, when dealing with more than two dimensions or large features, interpreting the data becomes very difficult for the researcher [208]. Glynn stresses that apart from the general difficulty of the methodology, researchers "should avoid fishing for results by randomly combining factors in the hope of finding correlations that could be interpretable" as this can increase the probability of finding irrelevant associations. This alternative may be useful but needs to be explored further and adapted better to the dichotomous nature of chronic condition variables for multimorbidity pattern purposes [47].

- Exploratory factor analysis: This was the method used for our assessment of multimorbidity. Exploratory factor analysis is a statistical technique used to summarize the correlation among a series of variables, with the expected aim of understanding the underlying structure of the data. The aim is, therefore, very similar to that of cluster analysis or multiple correspondence analysis. This method defines a set of underlying factors, in our case multimorbidity patterns, by estimating the relationship between the variables in each factor. Moreover, it allows distinct variables to be included in various factors, which is not the case with other methods such as cluster analysis. Firstly, a correlation matrix is needed to assess the correlation structure between the variables (chronic conditions in this case). Exploratory factor analysis requires continuous data, which is a limitation, but specific correlations can be used to avoid this problem. In our case, a tetrachoric correlation matrix was used due to the dichotomous nature of the variables, so that it is assumed that diseases included in our analysis have a progressive course and are diagnosed when they reach a certain threshold [209]. By using the results from the tetrachoric correlation matrix, the factor analysis technique leads to a certain number of factors but a selection of the statistically relevant ones is needed. In our case, the number of factors extracted corresponded to those with an eigenvalue of at least 1.0 [50]. Although this method is widely used, it has to be borne in mind that, depending on the research, the extraction could be based on priori criteria, use of a scree test, etc. For every selected factor, there is a factor loading value corresponding to

each of the variables. A specific condition is selected to form part of a pattern if its corresponding factor loading value was above a certain cut-off, 0.25 in our case, which indicates a stronger association [37,50]. Moreover, the Kaiser-Meyer-Olkin method was used to estimate the adequacy of the sample in the factor analysis, whilst cumulative variance was determined to describe the variance of the diagnostic data explained by the pattern. An oblique rotation (Oblimin) was performed to allow a better interpretation of the analysis factor.

We consider that exploratory factor analysis is an excellent approach for the investigation of multimorbidity patterns in the general population because: a) It allows a more thorough statistical analysis compared with the mere counting of chronic diseases or the observed/expected ratio; b) Chronic conditions can be present in several factors, unlike cluster analysis; c) it does not require complex management of data as is the case with principal correspondence analysis; d) there is some experience compared with other techniques, such as the principal correspondence analysis; e) it avoids subjective decisions based on complex visual interpretations such as dendrograms in hierarchical cluster analysis and plots in principal correspondence analysis.

A common limitation of studies dealing with any of the techniques mentioned above is that, due to the cross-sectional nature of the study, the kind of interaction between diseases cannot be evaluated, which requires a great deal of impartiality and evidence-based literature when interpreting the results. Thus, discovery of multimorbidity patterns implies that further study is needed to assess direct causality, associated factors or heterogeneity-causality to better design prevention or care management programs.

4.1.4. Association between physical and mental conditions

Apart from the multimorbidity patterns, we also searched for individual associations between physical and mental conditions. This issue is especially relevant as the elderly suffer from a very high prevalence of chronic conditions and the impact of this association may be crucial in terms of quality of life. There is evidence of this association for specific conditions but further research was needed, especially in Spain, where the available information is very scarce [210]. Our results show that asthma, angina, chronic lung disease and arthritis were associated with depression in the binary logistic regressions after adjusting for covariates. Only angina showed a clear association with anxiety after adjusting for covariates. These associations have been highlighted in previous studies [211–214]. There are some hypotheses to explain these findings. Firstly, arthritis, angina, chronic lung disease and asthma present

with unpleasant symptoms such as joint pain, chest pain or shortness of breath, whereas cataracts, diabetes, hypertension, edentulism or stroke are mainly asymptomatic [68,215]. Moreover, these diseases may be linked to greater disability, leading to isolation or frustration [216]. Other explanations include the possible effects of pro-inflammatory cytokines, platelet activation, disturbances in the autonomic nervous system or hypothalamic-pituitary-adrenal axis dysfunction [211]. Our results also support the findings in the meta-analysis by Huang et al, where hypertension was not associated with depression [210]. It should be noted that previous studies also found other relationships, such as diabetes with depression in the World Mental Health Surveys study [189]. This association is controversial since Huang et al found that prevalence, but not incidence, of depression was associated with the presence of diabetes [217]. Further research is needed to assess the directionality of these effects and confirm other specific relationships. In addition to co-occurring pairs, the number of physical conditions was also associated with higher prevalence rates of depression and anxiety, highlighting the importance of co-occurring chronic conditions. The limited evidence that exists in this respect, is in agreement with our findings [218].

4.1.5. Implications of multimorbidity in healthcare

As stated before, co-occurring chronic conditions have been associated with poor health outcomes and high healthcare-related costs. To date, however, research on this topic has been insufficient, despite increasing interest over recent years.

One of the most important implications of discovering certain multimorbidity patterns in the general population is that clinical guidelines could benefit from this and general care could be adapted by taking them into consideration. One might expect current guidelines to address comorbidity and multimorbidity since about two thirds of the population over 65 years suffers from it. However, this is not the case. Guthrie et al, in his analysis of clinical guidelines and multimorbidity, showed an example of an older person in the USA suffering from co-occurring diabetes, arthritis, osteoporosis, hypertension and COPD [69]. The assessment of the guidelines of those five highly-prevalent conditions resulted in only one of them acknowledging potential comorbidity. Moreover, the information provided was contradictory and the recommendations for the patient were considered unfeasible by the authors. A similar study was conducted in United Kingdom by Hughes et al [219]. In this case, the National Institute for Health and Care Excellence (NICE) clinical guidelines for diabetes, secondary prevention for patients with myocardial infarction, depression, COPD and osteoarthritis were analyzed. Comorbidity was inconsistently addressed in the guidelines. A

few relevant comments were made with that regard and most were of a general nature. The author concluded that there was need for “guidelines for people, not for diseases” suggesting that a better approach was essential. The relevance of this issue was highlighted in 2012 by the then chairman of the NICE, Sir Michael Rawlins, who announced it was one of his priorities to include multimorbidity in guidelines [220]. However, in 2014, the NICE had to recognize again the need to shift the emphasis to multimorbidity guidelines rather than single-condition guidelines, which indicates that there was a lack of supporting evidence despite the intention to provide new guidelines covering multimorbidity issues [221]. Thus, providing reliable evidence on multimorbidity patterns is an essential step in understanding the distribution of chronic conditions in the general population. With this information, other studies, especially longitudinal and interventional studies, should be encouraged to aid the drawing up of recommendations. Guidelines should also take into account polypharmacy, especially for frail patients and the cognitively impaired, and the need for certain treatments in patients with limited life expectancy.

It seems clear that the care of the elderly needs to involve interventions to address multimorbidity globally. Smith et al reviewed the interventions in managing patients with multimorbidity. These interventions covered four perspectives: professional, financial, patient-oriented and regulatory affairs [222]. As interventions taking multimorbidity into account appeared to be more effective for specific functional difficulties or specific risk factors, the authors concluded that it is vital to identify multimorbidity patients and develop cost-efficient interventions for them [222]. These results and conclusions underlines the usefulness of our and similar studies as starting points, but also highlight the need to assess the impact of chronic conditions on functioning and quality of life (this issue will be discussed in section 4.3.) [223]. Additionally, there is a need to include multimorbidity patients in trials and observational studies to support evidence-based care [223]. From a healthcare cost perspective, it is important to develop programs including interventions that target patients. Up to now, there have been mixed results in that respect but the potential cost savings may be significant [222]. In this context, communication and coordination of care results are essential, while the patient is expected to play a more active role in the management of their own care [224,225].

Finally, it is worth highlighting the apparently bidirectional relationship between mental and physical conditions and bearing in mind that “there is no health without mental health” [226]. In our study, interesting associations were discovered. First, there is a multimorbidity pattern including anxiety, depression and arthritis, as discussed above. Moreover, the study of

independent associations between pairs of diseases showed a statistically significant association between depression and the following chronic physical conditions: asthma, angina, chronic lung disease and arthritis. In that regard, Mercer et al stated that "practitioners must always consider mental health issues in patients with long term physical conditions", especially if these conditions impact on self-management and coping skills [226]. Palliative care also needs to be specifically addressed in the case of multimorbidity patients [227].

4.2. Visual impairment and chronic conditions

4.2.1. Visual impairment and eye care in Spain

Our results show a clear decrease in the values of objective (distance and near) visual acuity with age in the overall adult population. This trend begins in middle-aged adults. There are reports of moderate prevalence of the most relevant ocular disorders in the population aged between 50 and 60 years. For instance, data from the Framingham Eye study (USA) showed the presence of aged-related lens changes in 42% of people aged 52-64 [228]. Congdon et al showed a prevalence of nuclear cataract (13.2%), posterior subcapsular cataract (1.8%) and cortical cataract (8.0%) in the population aged 50-59 years [229]. Furthermore, the highest incidence of presbyopia (first-reported effects) appears in people aged 42 to 44 years old [230]. With regard to glaucoma, over 3% of the population already suffers from angle closure or open angle glaucoma in Europe at the age of 57.5 years [231]. Other conditions, such as age-related macular degeneration or diabetic retinopathy, have also been clearly associated with age. Near visual acuity showed the greatest changes across age in our study, mainly due to the presence of presbyopia as it appears in the whole population at a certain age. In the population aged over 65 years, only 33.8% of women and 43% of men achieved the highest scores on near visual acuity. Mixed results were observed with regard to sex. Women were found to have worse objective near visual acuity. Similar trends were found with regard to "subjective" assessment of distance and near vision across age. In this case, women showed worse subjective distance visual acuity than men.

There are some considerations to be taken into account when interpreting the results. In our study, a high prevalence of low vision (regardless of the prevalence of ocular diseases) was found compared with other studies performed in a clinical setting (where prevalence is lower). We found about 17% and 40% of distance and near visual impairment in the 50-64

years subgroup, respectively. In several similar country-representative reports of the WHO's SAGE study, prevalence of distance and near visual impairment reached up to 20% and 60%, respectively, in the younger subgroup (50-59 years) [232]. In epidemiological studies, such as the COURAGE study, the main aim is to observe general trends and analyze them in their context. We carried out visual acuity tests and subjective visual assessments that allow us to analyze this information but there is no formal diagnosis of low vision since the assessment conditions are not totally comparable with an ophthalmologic/optometrist clinics. Thus, data cannot be compared with studies using a more clinical approach. For example, Keeffe et al presented, in the WHO bulletin, a simplified screening test to identify people with low vision in epidemiological studies where they stated that their tests aimed to provide screening results and to establish basic information on functional vision, not a clinical diagnosis [233]. Thus, we consider that our results are comparable with other similar epidemiological studies, such as the SAGE study, but researchers and stakeholders should analyze the data with caution when comparing them with some national data or specific clinical studies.

Regarding general eye-care issues, our study found worst performance in women. They used more distance and near glasses, had worse objective near visual acuity and worse subjective distance and near visual acuity with their usual correction. Other studies have found that poorer results in vision occurred in women, therefore our results highlight the need to promote visual assessments, especially in elderly women [234]. Age differences were found with regard to the use of glasses, objective visual acuity and subjective acuity. It was observed a larger proportion of population over 65 years having their last visual check during the last 12 months compared with younger groups, but it was only 35.5% in men and 37.6% in women. The relevance of vision loss may be even more important in the elderly, as spouse vision impairment in older couples also impacts negatively on the partner's well-being, physical functioning, social involvement and mental health [235]. There is a need to increase rates of visual assessment in the elderly taking the impact of visual loss on quality of life and disability into account, which in some cases may benefit from optical correction, medical treatment or interventions to enhance social participation [236]. This is especially relevant considering the low proportion of near visual impairment in our results, which may be related to presbyopia in most cases, that can be corrected.

4.2.2. Visual impairment and chronic physical conditions

Our study has shown a clear relationship between the presence of various co-occurring chronic physical conditions and poorer distance and near visual acuity after adjusting for

covariates. For example, the OR for distance visual impairment reached 2.83 (95%CI: 2.23, 3.58) in the population with 3 or more chronic conditions compared with those with no chronic conditions. Thus, multimorbidity could be considered a shared risk for visual impairment in older adults as the co-occurrence of chronic conditions affects a large proportion of this population group. This may be especially relevant as visual impairment has been associated with poorer results in disability and quality of life [73,76,237].

To the best of our knowledge, our study is the first that has analyzed the association between the presence of co-occurring physical conditions and visual impairment, highlighting the additive effect of chronic conditions. There are authors, such as Whitson et al, that previously included variables related to those in our study but they assessed the impact of visual impairment and cognition on disability (multimorbidity is used as a covariate to assess their impact on disability) [90]. Others, such as Brody et al, specifically assessed the association between one single visual disorder (not visual performance) and depression [95]. They also used Spearman correlations between comorbidity (2+ chronic diseases) and disability, not between comorbidity and vision. Another example is the study by Lamoureux et al where they presented some information regarding non-ocular comorbidity across visual impairment in the sociodemographic table, although this cannot be considered a paper focusing on this issue [87]. Some descriptive information on chronic conditions and visual impairment has been published but this was a descriptive analysis [238]. Finally, our study is not only the first to assess this association but also the first to provide reliable and comparable information for future studies as we have used very clear standard definitions for chronic conditions, mental disorders and cognitive functioning, previously used in large epidemiological studies (e.g., SAGE).

The underlying mechanism responsible for the additive effect of chronic conditions on visual impairment is unknown. There could be an analogy with frailty, a state in which the accumulation of deficits increases vulnerability to adverse health outcomes, so that additive co-occurring chronic conditions would lead to a higher risk of visual impairment [239]. In this context, individuals with several simultaneous chronic conditions, such as COPD, diabetes, hypertension or arthritis, may have a cumulative risk due to biochemical, inflammatory, vascular or neurodegenerative pathways. Previous studies have assessed some of these relationships. For example, diabetes mellitus is associated with retinopathy and cataracts, while arthritis has been associated with a higher prevalence of cataracts [86,203,240]. Moreover, it is known that there are risk factors other than diabetes that impact

on the risk of suffering from retinopathy, such as hypertension and hypercholesterolemia, so that cumulative effects, according to the literature, are possible [241,242].

Arthritis, stroke and diabetes have been found to be associated with poor visual acuity. Suffering from arthritis was associated with a higher odds of distance visual impairment (OR: 1.79; CI: 1.46, 2.21). There is little evidence on the association between arthritis and vision loss, which is poorly understood and may be multifactorial. Extra-articular arthritis symptoms may include conditions directly associated with vision loss, such as ulcerative keratitis, scleritis, uveitis and severe Sjögren syndrome [243,244]. Moreover, some drugs commonly used in arthritis treatment, such as glucocorticoids or chloroquine/hydroxicloroquine have been associated with a higher risk of developing glaucoma, cataracts and retinopathy [245–248]. With regard to the relationship between osteoarthritis and visual impairment, no clear evidence has yet been found. There is little epidemiological evidence on this issue, although Kirchberger et al suggested recently that patients with joint diseases had a higher risk of eye diseases [50]. Stroke was associated with higher odds of distance and near visual impairment (OR: 1.59 [CI 1.05-2.42]; OR: 3.01 [CI 1.86-4.87]). Stroke involves a wide range of sequelae, including low vision, quadrantanopia, hemianopia and motility disorders. However, there is little evidence at an epidemiological level [249]. Low vision may occur as a consequence of vascular pathology or other ocular abnormalities [250]. In fact, we hypothesize that ocular abnormalities affecting vergence and accommodation of the eye, which requires CNS coordination, would be responsible for the higher odds in the near vision results. In a previous study, Rowe et al reported that up to 92% of stroke patients had some form of visual impairment [249]. Our results underline the importance of this association and highlight the need for visual healthcare after stroke. Finally, diabetes was found to be related to a higher odds of distance visual impairment, as expected, but not to near visual acuity. Adjusting for the time from the onset of diabetes may impact the results so higher odds would be found in long-term patients, but this information was not available in our study.

4.2.3. Visual impairment and mental disorders

Our results showed a significant association between subjective visual impairment and major depression, in both distance and near vision (OR: 1.61 [CI 1.14-2.27]; OR: 1.48 [CI 1.03-2.13]). As mentioned previously, there is some evidence suggesting an association between visual impairment and depression in working-age adults [89,91]. There have been, however, mixed results in terms of the study of this association in the elderly. Of the 24 papers addressing this issue considered in the literature review, 13 found no association while 11 found a

statistically significant association. A high degree of variability is present in these and other studies focusing on this association. On the one hand, differences among them emerge regarding the type of visual assessment: visual acuity tests, medical records, presence of age-related eye-diseases, participants' self-rating, high contrast vs low contrast, vision-loss severity with functional screening, etc. On the other hand, various approaches have been used for the diagnosis of depression (GDS-15, CES-D, Goldberg, HADS-D, etc.). Moreover, most of these studies had small or relatively small samples. Thus, a need was identified to provide reliable data using a nationally-representative sample of the older adult population using standardized definitions and a complete assessment of visual functioning.

In addition to objective distance and near measures, the importance of the degree of subjective impairment experienced by the person with visual problems has been highlighted [251,252]. For example, Zhang et al found in a sample of 10,480 U.S. adults that self-report visual impairment was associated with depression whilst this association was not present with regard to objective measures (visual acuity test). These results are similar to ours [89]. Self-experienced visual loss may be critical as this leads to functional decline, disability and both communicative and social isolation [91,253–256]. Moreover, the Health Care Policy and Research Cataract Surgery Guidelines suggested that the degree of functional disability should be considered as an important indication for cataract surgery rather than mere objective visual assessment [257,258]. Differing trends between objective and subjective visual impairment regarding depression could be affected by the negative perception these patients might have of themselves. Consequently, we decided to test both objective and subjective visual functioning and assess any differential behavior. We found a stronger association in the case of subjective visual impairment, which highlights the importance of self-perceived impairment in this population group. Although we theorize that subjective visual impairment would lead to depression in these individuals, it may be that some depressed people had a higher tendency to complain about vision.

In contrast with the case of depression, no association was found between visual impairment and anxiety. This result is in the same vein as findings in previous studies in younger adults or elderly populations [92,102,103,110,116,259,260]. There has been, however, some controversy as a few studies have found an increased risk of anxiety when suffering from visual impairment and a high rate of anxiety in the population with certain ocular conditions has also been observed [72,101,109,112]. In our opinion, our study adds relevant information on the relationship between vision and anxiety as the evidence on this was scarce and there were some methodological issues that needed to be addressed. In general, there has been

variability in the definition of anxiety; sometimes it is not very clearly defined at all, while other studies used non-specific variables, such as “concern about blindness”. In our case, we used the World Health Organization’s Composite International Diagnostic Interview (CIDI questionnaire), a comprehensive, standardized tool which reinforces the reliability of our results, and which has also been shown to be useful in cross-cultural epidemiological studies [261]. For the all the above reasons, and the fact that we included both distance and near assessment, we believe we have provided a general evaluation of the impact of visual performance on anxiety, which will be comparable with other studies in the future.

4.2.4. Visual impairment and cognitive impairment

Cognitive functioning was found to be significantly associated with distance and near vision performance, both at objective and subjective levels. This association was stronger in the case of subjective near vision (OR: 2.40; CI95%: 1.52, 3.71).

Some studies have shown a statistical association between visual functioning and disorders that lead to cognitive impairment to some extent, such as Alzheimer’s disease and Parkinson’s disease [262–264]. In the case of Alzheimer’s dementia, some eye changes have been reported to occur along the disease course. Chang et al summarized the possible changes: protein deposition in the retina, retinal neurochemistry deficiency, and structural changes at several levels (retina and optic nerve, blood vessels and retinal microcirculation, crystalline lens) [120]. Further research is needed regarding these postulated mechanisms. From the perspective of visual tests, contrast sensitivity seems to be altered in these patients while there is no clear relationship between visual acuity and Alzheimer’s disease that would justify screening with visual acuity tests [120].

There are studies focusing specifically on cognitive functioning where mixed results have been found [121,122,265–268]. Sloan et al found a statistically significant association between vision decline and cognition, but the effect size was considered small [121]. Elliott et al found a relationship between cognitive impairment and near visual acuity but not distance visual acuity, which highlights the need for comprehensive studies, including both distance and near vision assessments [122]. Very little information is available with regard to subjective visual performance. To the best of our knowledge, only two studies used subjective assessment and none compared both types of measure to check differences between them [121,266]. As such, research should include evaluation of subjective visual perception to provide a complete picture of the association. In our study, we showed that there is association both at subjective and objective levels, which seems to be slightly stronger in

subjective vision. The mechanisms responsible for the interaction between cognition and vision are not clear. On the one hand, visual impairment may lead to deprivation of sensory input, which in turn would lead to functional or structural cerebral changes. On the other hand, it may be plausible that common physiological pathways were involved. For instance, impairment of the ventral/dorsal pathways and a loss of retinal ganglion cells has been described in Alzheimer's patients [262,269]. From a more theoretical perspective, cognitive slowing was observed when simulating visual impairment, especially in the elderly [270,271]. In addition to causal and etiopathogenic concerns, the association between vision and cognition should be underlined as their coexistence is related to greater risk of disability [90].

4.2.5. Implications

As mentioned above, visual impairment has been found to impact on several health outcomes such as quality of life, risk of falling, social participation and increased mortality [71–78]. Since progressive visual loss occurs with age, management of the population with eye diseases is critical. The World Health Organization estimates that 80% of all visual impairments can be corrected or are preventable [85]. Although national differences may emerge, it is known that adjusted glass prescription, but also timely cataract surgery or AMD intravitreal pharmacotherapy, would prevent functional visual impairment [84].

In Spain, the frequency of visits to the eye doctor has been found to be low, which could lead to an unmet need for glass prescription for individuals with less frequent visits who are not aware of their eye problems. Apart from glass prescription issues, other delayed treatments would be required to correct, prevent or stop progression of particular eye problems, which also reinforces the importance of regular visits to eye clinics [84]. The fact that more visual problems are found in distance vision could be partially interpreted as a need for glass prescription changes, which could be detected by means of eye tests. Thus, national efforts should promote periodical eye screening in the elderly, adjusted for risk factors (e.g., annual, biannual, etc.). The economic crisis in Spain may be mentioned in this context. On the one hand, regular visitors to the eye clinics mostly go to private eye clinics, which could experience lower attendance during times of economic difficulties. On the other hand, pharmacological treatments for some eye diseases (e.g., diabetic retinopathy, age-related macular disease or retinal vein-occlusion) involve expensive medication, so it is uncertain whether delay or treatment-selection issues are present.

Cost-effective eye-screening planning should not only consider the age of individuals but also situations in which it is known that there is an increased risk of visual impairment. This is

the case with diabetes, arthritis and stroke, according to our results. Moreover, increasing odds of visual impairment has been found in both distance and near vision as the number of co-occurring conditions rises. Thus, multimorbidity patients should receive special attention. Additionally, prevention issues arise in the context of physical conditions. It is known that tight control of diabetes, but also blood pressure and, in all likelihood lipid control, are associated with fewer retinal problems in diabetic patients [272]. In our case, diabetes was independently associated with visual impairment but no information was available on the glycaemic control of the patients to assess this effect thoroughly. Future multimorbidity guidelines or single-disease guidelines that include information on multimorbidity should include evidence-based recommendations for prevention taking risk factors into account. Diabetes guidelines are an example in that respect. As ocular diseases are well-documented in diabetic patients, recommendations already exist in Spanish guidelines; e.g., biannual eye screening in case of mild nonproliferative retinopathy [273]. However, there are no clear screening recommendations for most visual disorders to guide clinicians [274].

With regard to mental health, depression, but not anxiety, was associated with visual impairment. As stated above, more complex mechanisms may be involved in this association compared with physical conditions. The association is particularly interesting as it has been associated with increased risk of falls and lower quality of life [275,276]. The fact that the association was present only in subjective vision evaluation highlights the need to expand the evidence on this specific assessment. If confirmed, easy subjective screening vision tests could be performed in primary care or eye-care settings as a proxy measure to detect patients at risk of developing depression. These patients would require some basic monitoring and periodical depression screening. Some authors have proposed instruments, such as the Patient Health Questionnaire-2, to assess depression risk in eye-care settings [277]. Healthcare professionals should be aware of this association and its implications. Rees et al underlined the need for further training of health professionals in identification and treatment of depression in patients with vision impairment [278,279]. Management of visual loss may tackle the vision-specific distress suffered by these patients [280]. For example, stepped-care has been proposed to prevent depression in visually impaired older adults [281].

With regard to cognitive functioning, our results showed a clear association between cognitive impairment and vision loss. The clinical interpretation of this association is complex because there is a need to understand the pathophysiological mechanisms leading to these results. If visual impairment were a factor involved in cognitive impairment, visual screening would be useful in detecting and managing progressive cognitive decline with age.

This could then help to delay progressive, visual-related cognitive impairment. (This interpretation takes the aforementioned association between simulated visual impairment and slowing of cognitive performance into account) [270]. However, visual screening does not seem to be useful as biomarkers in Alzheimer's disease judging from the evidence available in the review by Chang et al [120]. Consequently, our results shed light on the association between vision and cognition but further studies are needed to recommend specific screening or management of these patients.

4.3. The association between chronic conditions, disability and quality of life.

4.3.1. Chronic conditions and disability

Our study shows a clear association between chronic conditions and disability. This association is present for conditions individually but turns out to be especially strong as the number of co-occurring conditions increases. Furthermore, our study also shows relevant trends according to gender in this association.

The results of the multiple linear regression showed that all conditions except hypertension were associated with disability. It is remarkable that mental disorders (depression and anxiety) and stroke had the highest impact on disability: depression (β: 15.70; 95%CI:13.62,17.77); anxiety (β: 11.17; 95%CI: 2.49,19.86); stroke (β: 12.15; 95%CI: 8.08,16.22). There is some evidence suggesting the considerable contribution of mental disorders to disability [148]. For instance, Martin et al showed the growing importance of depression in the United States, although it was not found to be among the leading causes of disability [282]. Another study by Merikangas et al found that mental disorders had the greatest impact on disability, after musculoskeletal disorders, in the United States [283]. Nevertheless, studies to date have tended to exclude mental disorders when analyzing the impact of chronic conditions, so further study was needed to assess this relationship [146,149]. Our results underline the importance of mental health in the elderly at this level. Stroke is the physical condition with the highest impact on disability, followed by COPD, arthritis and angina, which have been previously associated with poor health outcomes [146,149,284–289]. These physical conditions share some similarities, such as disabling symptoms (pain, shortness of breath, etc.) and physical limitations, whereas asymptomatic conditions such as diabetes or edentulism had a lower impact on disability. Diabetes has shown mixed effects on disability in previous studies [151,290,291]. For example, Taş et al found no association between diabetes and disability in Holland, and Okochi (2005) found no association between

diabetes and severe disability in Japan [151,290]. Kim et al found this association only for those participants aged 70 to 79 years of age in a sample of participants aged 65-89 in South Korea [291]. A recent review by Wong et al concluded that diabetes is strongly associated with physical disability. However, they excluded those studies reporting disability as a continuous measure [123]. They justify this by maintaining that cut-offs for disability are artificial, depend on the tool and would introduce bias into the final results. Moreover, the review focused on physical disability only and the selected studies did not adjust for other chronic conditions. Thus, further investigation is needed to clarify this association. Mixed results have also been found for hypertension in previous studies [151,292,293]. Our results suggest that asymptomatic conditions impact less on disability than symptomatic ones.

With regard to co-occurring pairs of conditions, two interactions were selected for study (depression*anxiety; cataract*diabetes) after the assessment of the pairs. Suffering from diabetes and cataracts resulted in a synergic effect on disability. Caution should be exercised in the interpretation of this result. Duration of diabetes and parameters reflecting its poor management, such as high levels of fasting blood sugar, HbA1c or macroalbuminuria, are strongly related to the prevalence of cataract [294,295]. Poor control of diabetes, also related to other metabolic syndrome complications, would result in poorer health status and a higher degree of disability compared with the mere addition of the individual burden of cataracts and diabetes. Co-occurring depression and anxiety resulted in a ceiling effect but this was not statistically significant.

At a cumulative level, a sharp increase in disability was found when more chronic conditions were present, with estimates of the β coefficient ranging from 3.57 (95%CI: 2.56, 4.56) in respondents with one condition up to 27.64 (95% CI: 24.99, 30.29) in patients with four or more conditions. Our study complements the evidence on this issue since most studies have previously focused on the impact of single conditions, specific pairs or organ classifications [148,149,284,285,292,296–298] whereas the number of articles focusing on multiple chronic conditions is low and there is great methodological variation [146,299–303]. The few studies assessing multiple chronic conditions have used the number of conditions due to the valuable information provided, the generalizability of the results and the simplicity of interpretation. For instance:

1) Binary variable of >1 chronic condition *vs* none: Basu et al; Fox et al; Alfonso Silguero [300,301,303].

2) Number of chronic conditions: Hung et al; Alfonso Silguero et al; McDaid et al [146,299,302,303].

The association between the number of chronic conditions and disability rates found in our study suggests that multimorbidity patients require special attention. Disability per se predicts future disability status. Thus, it is important to identify high-risk groups needing preventive, curative or palliative strategies [151]. A recent Cochrane review concluded that patients at risk can benefit from intervention programs, such as resistance strength training, or preventive home-visitation programs [304]. However, more evidence is needed on the long term effects and adverse events of these programs.

Comparison of our results with other studies is complex due to the variety of approaches previously used to assess disability. Classically, tools and indexes assessing disability have focused on the ability to perform either activities of daily living (ADLs) or instrumental activities for daily living (IADLs). For example, the Katz index is one of the most common ADL tools, including issues such as feeding, continence, transferring, toileting, dressing and bathing. Tools assessing IADLs (e.g., Lawton index) focus on more complex activities such as heavy housework, shopping, using transportation, preparing food, etc. [130]. These and other indexes, such as the Barthel index, are useful instruments that have been implemented in the clinical setting, especially in nursing, but certain aspects including social impact cannot be assessed. The World Health Organization developed the International Classification of Functioning, Disability and Health (ICF), a biopsychosocial model that works at three levels (body, individuals and society) [70,305]. Disability is a broad-spectrum term that covers impairment, activity limitation and participation restrictions in which the role of contextual factors is widely recognized [124]. In this respect, a comprehensive tool developed under the ICF scheme was used to design the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) [306]. The interpretation of our results has to be considered in the context of the use of this tool, therefore comparison with other indexes or tools would not be appropriate. In our case we used the 12-item, validated version of this tool [131]. WHODAS 2.0 has proved to be particularly useful as it has been previously validated in patients with chronic conditions [307]. Moreover, WHODAS 2.0 was designed for epidemiological purposes.

Very few studies in Spain have previously used WHODAS 2.0. As an example, Virués-Ortega et al used this tool in participants over 75 years only [306]. Although they recruited participants from several geographic areas, it was not a nationally representative sample and,

more importantly, they did not include chronic conditions in their analysis. Pedro-Cuesta et al assessed the impact of stroke, COPD and chronic heart failure patients in Madrid, concluding that disability among these patients is frequent, but they did not provide a comprehensive list of diseases nor the cumulative risk of conditions [308]. Almazán-Isla et al used this methodology to assess disability in a rural area in Spain. They did not assess the impact of individual diseases but found that a higher number of diseases increased the WHODAS score greatly (OR of having 4+ conditions was 2.97; 95%CI: 1.88-4.70) [308]. A few other studies have used distinct approaches, such as the Barthel index or other specific ADL tools [298,303]. For example, Alfonso Silguero et al found that stroke was associated with mobility loss, although this association was not found with other conditions individually or with the number of chronic conditions [303]. Valderrama-Gama et al found in a regional sample from Madrid, similar results to those reported in our study: cerebrovascular diseases, depression and anxiety disorders were the leading causes of functional disability [298]. Our study provides comprehensive, previously unavailable evidence on the relationship between chronic conditions and disability in Spain.

4.3.2. Chronic conditions and quality of life

As in the case of disability, quality of life was found to be greatly associated with single chronic conditions, and especially when they accumulate in individuals. Our study also showed relevant trends according to gender in this association.

The results from the multiple linear regression showed that all conditions except hypertension were associated with lower quality of life. Again, mental disorders (depression, anxiety) and stroke had the highest impact on quality of life: depression (β: -14.00; 95%CI:-15.85,-12.14); anxiety (β: -7.82; 95%CI: -11.57,-4.08); stroke (β: -8.16; 95%CI: -11.77,-4.55). Some studies have suggested an intimate association between mental disorders and quality of life [164,309,310]. As in other areas of medical research, a high proportion of studies did not include mental disorders when assessing the impact of chronic conditions [135,146,311]. The few studies available that have used a comprehensive analysis, including both mental and physical conditions, have shown this association [135,147,312–315]. Our results expand the evidence on this issue and shed light on this association in the Spanish population. As in the case of disability, stroke is the physical condition with the highest impact on quality of life, followed by COPD, arthritis and angina. Some studies found similar individual associations [146,289,316,317]. Physical limitations and disabling symptoms (pain, shortness of breath, etc.) are common in these conditions and are responsible for the higher burden associated with them. Conditions that are mostly asymptomatic, such as diabetes or

edentulism, had a lower impact on quality of life but still showed a significant association with poorer results in quality of life. Diabetes has been generally associated with poorer results in quality of life but there have been mixed results [135,311,312,314,315,318,319]. Our study suggests that the individual impact of diabetes on quality of life exists but is mild. Other conditions coexisting with diabetes, e.g., cardiac problems, would be responsible for the highest burden in terms of quality of life loss. As previously mentioned, hypertension was not related to worse outcomes. Mixed results have been found in prior studies focusing on this condition [135,309,311,312,314,315,318]. It has been found that symptoms are responsible for the greatest impact on quality of life in patients with hypertension, therefore treatment and patient monitoring would minimize the relatively few symptoms in participants with hypertension [320]. This has to be taken into consideration when interpreting our results, since diagnosis was reported by the participants. A high proportion may have been receiving medical care at the time of the interview and possible symptoms would be minimal. Our results suggest that symptomatic conditions are more likely to be associated with poorer results in quality of life.

With regard to co-occurring pairs of conditions, two interactions were selected for study (asthma*COPD; cataract*diabetes) after the assessment of the other pairs. Suffering from COPD and asthma resulted in inverted directionality of the results compared with the individual effect of these conditions on quality of life. This result did not alter the individual negative effect of COPD and asthma on quality of life and suggests that a ceiling effect appears when these diseases are present simultaneously. Both COPD and asthma are prevalent conditions in the elderly and there is a high frequency of overlapping diagnosis in the elderly. For example, over 50% of CODP patients aged over 80 years have co-occurring asthma [162]. Consequently, the asthma-COPD overlap syndrome has been defined and studied. As the name suggests, it involves features of both conditions and has been related to poorer results in quality of life in patients with asthma and similar to those found in COPD patients [321]. In our study, we found that 43% of the respondents diagnosed with COPD also suffered from asthma, which supports results previously found in the clinical setting. Mixed results have been observed with regard to the clinical outcomes of this syndrome. For example, Fu et al found, in a longitudinal study, that COPD or asthma patients had a worse prognosis than patients with the asthma-COPD overlap. In contrast, other studies have showed more severe exacerbations when these diseases occurred together [322,323]. Further research is needed to clarify the asthma-COPD overlap syndrome and its impact on health outcomes such as quality of life and severity of exacerbations.

At an additive level, a sharp decrease in quality of life was found when more chronic conditions were present, with estimates of the β coefficient ranging from -3.26 (95%CI: -4.66, -1.93) in respondents with one chronic disease to -18.10 (95%CI: -20.95, -15.25) in respondents with four or more conditions.

These results underline the relevance of multimorbidity to quality of life, while expanding and complementing previous evidence on the study of individual conditions, specific pairs of conditions or organ domain classifications [135,143,309,310,313,315,324,325]. There are a few studies that assessed the impact of multimorbidity on quality of life. These studies, as in the case of disability, used either multimorbidity as a binary or continuous variable, with great variability in their methodology [299,311,312,314,318,319,326,327]. Our results support the descriptive analysis by Lawson et al, which showed reductions in preference-weighted health-related quality of life in participants with longstanding conditions [299]. However, their results are not completely comparable for several reasons: conditions included in the analysis, number up to three conditions and the count itself allowed one condition for every organ-based classification group. Heyworth et al and Brettschneider et al assessed quality of life and its dimensions with the EQ-5D and found that it decreased with an increasing number of chronic diseases [312,328]. However, Heyworth et al restricted their study to six conditions, with no mention of mental disorders, while Brettschneider et al considered multimorbidity as a continuous variable and provided no information on the specific disease count. Thus, these results are complementary rather than comparable. Tan et al also found poorer results in quality of life with a higher number of chronic conditions but a ceiling effect seemed to appear between two and three chronic conditions [314]. These results diverge from those found in our study, with the group with four or more conditions having noticeably lower quality of life results compared with participants with three chronic conditions. Our results should help to target multimorbidity patients as a population subgroup in which clinical, community and patient-centered care should be prioritized to ensure the best possible quality of life [329].

Comparison of our results with those of previous studies is complex due to variability in methodology. A great number of tools can be found in the literature for the study of quality of life. The Short Form 36 (SF-36) is the most widely used tool for the assessment of health related quality of life or self-perceived health status [330]. Apart from some limitations inherent to the SF-36 tool, the fact that many of the questions are focused on functioning has been critized. As stated by Horner-Johnson et al “measures include questions on function, reflecting an assumption that respondents are unhealthy if they are unable to perform

certain functions such as walking or climbing stairs" [331]. With the development of the WHO's ICF, as previously mentioned, a more comprehensive approach is proposed to assess the health status and quality of life of the individual. According to the ICF definitions, people with some functional limitations can experience good health, implying that the SF-36 lacks the ability to reflect quality of life from a more global perspective. Horner-Johnson et al found that there was a possibility of measurement bias due to this limitation [331]. As such, we decided to use the modified version of the World Health Organization Quality of Life instrument (WHOQOL), called the WHOQOL-AGE, that provides a comprehensive result for quality of life and has been specially adapted for the elderly population [133]. This short-version contains 13 out of 100 questions from the original version and has been validated in populations over 50 years old. The COURAGE is the first study to date to use the WHOQOL-AGE instrument so no data is available for comparison in Spain or other countries. Despite this limitation, the validity of the measure will presumably ensure that future studies will use it and, therefore, allow comparison with our results.

4.3.3. Gender trends in disability and quality of life

Systematic gender-dependent errors in design and analysis of research are described in the literature due to androcentrism or gender insensitivity [332]. Assuming, incorrectly, equality or differences between women and men would lead to bias at several levels: selection, measurement, and analysis of the results [332]. Studies focusing solely on women or men, unless justified by previous research, would also lead to difficulties in terms of applicability in healthcare practice. Thus, a suitable approach has to be considered for each case. Previous research on the subject of our study has underlined the need to address disparities in risk and interventions across gender in the population suffering from chronic conditions [329]. Although gender is considered when adjusting regression models in most studies, only some provide descriptive results or separate analyses by gender, which in turn tend to focus on specific conditions rather than more comprehensive approaches to multimorbidity [149,150,288,291,325,333–335]. Consequently, our study covered the sample globally and also by gender.

Our results have shown some trends in the prevalence of chronic conditions across gender: a) higher prevalence of angina and COPD in men; higher prevalence of arthritis, depression, anxiety, cataract, and number of chronic conditions in women; c) no differences for hypertension, diabetes, asthma, stroke and edentulism. In the descriptive analysis, depression was found to be the condition with the highest impact on disability score (30.0; 95%CI: 25.3-34.6) and quality of life score (53.6; 95%CI: 51.0-56.3) in men in terms of mean

scores. In women, angina was the condition with highest impact on the disability score (36.9; 95%CI: 31.8-41.9) and anxiety on the quality of life score (48.9; 95% CI: 54.8-52.9). Higher disability and poorer quality of life scores were found in women than in men for most conditions. These results reinforce the idea that greater attention should be paid to women to prevent and manage poor outcomes in disability and quality of life. Additionally, it sheds light on the relationship between chronic conditions and these outcomes [291,336–338]. However, similar scores were found in both sexes for anxiety, asthma, depression and stroke (stroke only for quality of life). Both sexes showed similar behavior with regard to the number of chronic conditions, with a ceiling effect appearing when people reach a certain level of multimorbidity.

After adjusting for covariates, our study showed that women had higher risk of disability than men (β: 2.92; 1.72-4.12). The clinical relevance of this result is unclear as no clinical cut-offs for these screening tools are available to date. We hypothesize that the impact of gender on disability is moderate rather than intense since effect size resulted in small-moderate values. Moreover, the estimate of the β coefficient is comparable with the effect of some diseases, such as diabetes (β: 2.32; 0.56,4.08) or edentulism (β: 2.93; 1.19,4.68), but very low compared with depression (β: 15.70; 13.62-17.77) or stroke (β: 12.15; 8.08-16.22). Analogous results were found for quality of life.

The separate regressions for males and females showed similar behavior for chronic conditions as that reported in the global regression. For some of these conditions, however, the association disappeared in men or women. Asthma was related to poor results in quality of life and disability in men only, while anxiety was found to be associated with poorer results solely in women. Since the prevalence of anxiety in men was relatively low, we consider this result may be biased by the power of the study. Other conditions showed these differences in one of the outcomes only. For example, cataract was associated with disability and angina with quality of life in women only, while edentulism was found to be related to poor quality of life in men. With regard to the number of chronic conditions, a greater impact on quality of life and disability was found in both genders. These results suggest that the effect of conditions in each gender group may differ and should be considered in future studies. With regard to asthma, for example, the management of the disease in men should focus particularly on preventing loss of quality of life and physical functioning. To clarify the interpretation of these separate regressions by gender, interactions between each chronic condition and gender were assessed. Interactions were found in depression with respect to quality of life; and in diabetes, co-occurring cataract-diabetes, and the number of chronic

conditions with respect to disability. These distinct impacts by gender may be considered when interpreting our results. In our case we focused on the differences between the regressions. The inclusion of multimorbidity patients only would have been useful to improve the power of the study and provide more consistent information on the analysis of interactions and eventually further clarify cross-gender differences.

4.3.4. Implications

Multimorbidity impacts greatly on patients and healthcare systems. Individuals with multiple chronic conditions show increased health care utilization [339]. As the number of providers increase, their instructions become difficult to understand, remember and reconcile [13]. Moreover, they have to face complex treatments, which in turn can lead to side effects, morbidity and even worse disability and quality of life [340]. These results can also be found when prescriptions by different physicians are made while ignoring other co-occurring conditions. Multidimensional health outcomes such as quality of life and disability are useful as global measures of wellbeing and health status in the population [12]. In the context of financial shrinking, healthcare providers should aim to increase life span cost-effectively while maintaining quality of life and functional ability.

Our study highlights the relevance of both individual and multiple chronic conditions to disability and quality of life. Most of these conditions are preventable or can at least can be delayed with proper actions. This is an area that should be explored since 97% of health expenses are presently spent on treatment while only 3% is invested in prevention [12]. For example, intensive lifestyle modification, bariatric surgery, and anti-diabetic and cardiovascular medications were found to be effective in the prevention of Diabetes mellitus type 2 in a recent review by Merlotti et al [341]. With regard to stroke, a higher risk is present in people with certain conditions (e.g., atrial fibrillation) which should be properly managed but there are also risk factors that could be prevented (e.g., obesity, smoking, hypertension, physical inactivity, etc.) [342]. These considerations are applicable to other conditions (e.g., angina, hypertension, COPD, etc.) so greater efforts should be made to implement extensive prevention plans in the elderly and measure their impact.

Once a condition is established, health policies should consider those modifiable/correctable conditions and treat them in a timely fashion (e.g., cataract, edentulism). In the case of cataract, not only quality of life and disability would be expected to improve. These interventions have further implications, as cataract surgery may promote longer overall survival according to some studies [343]. The population with edentulism suffers from

negative perception which leads to poor social interaction and lower quality of life in addition to diet restrictions associated with cardiovascular diseases, diabetes, etc. [159]. Prevention of dental loss and proper management of oral health is fundamental since each tooth that remains after the age of 70 is associated with a decrease of 4% in mortality over 7 years [159]. In Spain, there are long waiting lists for cataract surgery while dental care is mainly provided by private dental care providers, which could be related to delayed care or unaffordable treatments for patients. We hypothesize that early management of cataract, edentulism and specific cases of osteoarthritis would be cost-effective in terms of quality of life, disability and other health outcomes. Further research would be needed to address priorities in this respect.

Apart from the medical approach required for the management of chronic conditions, additional efforts should be made to prioritize actions in those situations with poorer outcomes. For example, the number of chronic conditions has been found to be strongly associated with poor quality of life and more disability. Patients with multiple chronic conditions could be a target group for periodical screenings aiming at early detection of quality of life and disability problems. Action could then be taken consequently (psychological support, physical training, social support, changes in the current treatment, etc.). For instance, patients at high risk could benefit from interventions (e.g., progressive resistance strength training) that have been found to be useful in preventing further disability [304]. Another target group requiring close monitoring could be those with mental disorders (depression, anxiety) and stroke, according to our results. However, single-disease management should be restricted to very specific circumstances with increased emphasis on multiple cluster associations to prevent fragmentation and duplication of services [13].

Along with these issues, some approaches aiming to improve health outcomes have been suggested at several levels. Nursing care management could be positive in terms of quality of life, patient satisfaction, self-care, drug adherence, service use and objective clinical measures [344]. This service would be very useful in unplanned, poorly coordinated or exacerbation-focused care [344]. A recent Cochrane review showed that specific functional difficulties should be targeted in multimorbidity patients to provide comprehensive care [345]. Telehealth care is a potentially beneficial approach. According to the recent review by Jones et al, telehealth care has showed similar or better health outcomes, including quality of life, for a wide range of chronic conditions [346].

4.3. Strengths and limitations

The main strength of our study is that results are extrapolated to the entire Spanish older adult population due to the sampling methodology applied. In the future, comparison will be possible with other countries including those in the COURAGE study (Finland, Poland, and Spain) and the SAGE study (China, Ghana, India, Mexico, Russia, and South Africa). The SAGE study is an ongoing program led by the World Health Organization with the goal of obtaining comprehensive longitudinal information on the health and well-being of adult populations [232]. Variables in this study were carefully selected to provide quality data, including validated algorithms and tools such as the aforementioned WHOQOL-AGE and WHODAS. The COURAGE study is a project carried out by several European institutions and the World Health Organization that used the same methodology as the SAGE study [347]. Moreover, we consider that comparability will also be possible with other studies that use these tools in the future. Additionally, longitudinal data will be available in the future as the Spanish cohort of the COURAGE is followed. The inclusion of depression and anxiety in the results and analyses also needs to be highlighted as previous studies have omitted mental disorders on most occasions. Thus, our work provides a more comprehensive picture of multimorbidity compared with most of the literature. Diagnoses were based on self-report by the participants but symptom-based algorithms were also implemented for symptomatic conditions (angina, arthritis, asthma, cataract, COPD and stroke) to collect information from participants that were not aware of their illness, or in the case of elderly people who forget or misinterpret their diagnoses. This allows a clearer picture of the participants to emerge compared with other studies. This may have led to higher sensitivity at the expense of lower specificity. The use of CIDI questionnaire, a validated and commonly used tool to assess mental health, is another strength of our study [261].

Our study has several limitations. Its cross-sectional nature identifies associations but does not allow cause-effect relationships to be determined. In our case, clinical expertise may help to overcome this problem in some cases (e.g., chronic conditions are logically responsible for lower quality of life, and not vice versa). Moreover, age effects may not be distinguished from cohort effects. Longitudinal studies are needed to better understand these associations. Multimorbidity research would benefit from standardized inclusion and conceptualization of diseases [31,50]. In some other cases, the Expanded Diagnosis Clusters (EDC) adapted from the ACG® system was used. This broad approach is more exhaustive but complex to conduct outside clinical settings or in the case of poor integration of health care levels [37]. It is known that studies assessing a similar number but different conditions make comparison

difficult [50]. Furthermore, the choice of which chronic conditions are assessed is also relevant as a higher number of included conditions logically results in a higher proportion of multimorbidity [31]. In our case, the selection of conditions was done according to the WHO's SAGE study, focusing on a limited number of highly prevalent conditions that constitute major causes of disability. This methodology allows the work to be conducted across countries. There is, however, a need in future studies to include diagnoses of other common conditions known to have a considerable impact on health care resources, disability, quality of life and mortality. According to the review by Prados-Torres et al, other diseases may be included such as malignancies, congestive heart failure, anemia or dementia [47]. The self-reported diagnoses and subjective assessments could bias the results compared with data from clinical records but this effect would be minimal as an acceptable correlation between self-reported and medical-record diagnosis has been found [348,349]. In the case of visual assessment, we checked the kappa results for objective and subjective visual acuity to confirm the differing behavior of the variables. Consequently, we checked this separately for mental health and cognition since subjective feelings are also supposed to be strongly related to those variables. Our study did not consider the progression and severity of conditions, which would be advisable in future studies. For example, severe COPD cases may be related to poorer health outcomes [350]. With respect to visual assessment, future studies should include binocular measures of visual acuity and other visual tests (glare disability, contrast sensitivity, etc.). Age selection could potentially skew results in the case of visual impairment, since its prevalence increases with age. Thus, we performed sensitivity analysis with participants over 65 years and compared them with our analysis (over 50 years), producing similar results. Additionally, poorer results in cognitive functioning have been described in patients with vision loss when the tests require vision tasks [351,352]. In our study, only verbal memory tests included a reading part. If the respondents had reading difficulties, the interviewer read the words aloud to minimize bias. In the analyses to assess the impact of chronic conditions on disability and quality of life, specific pairs were considered according to their high prevalence and high degree of interaction shown in the multimorbidity index. Further studies should include other combinations to deepen knowledge of less common co-occurring conditions [44]. There is a possibility that some respondents who did not take the medication prescribed by their doctors stated that they were not receiving treatment and were incorrectly classified as "not suffering from a specific disease". This limitation is minimized since the question was quite open "did you receive treatment…", rather than asking whether they were "taking the medication" and due to the inclusion of the symptoms algorithm in most conditions. Moreover, our study did not include the medication list or the

current number of medicines taken by the respondent. It would be useful to include this information in future studies since polypharmacy may be related to considerable impact on health in the elderly (morbidity, side effects, disability, etc.). Geopolitical context is another limitation. Specific results for an individual condition may vary according to external factors [353,354]. Financial crises may impact some results, such as the prevalence of mental disorders. However, recent evidence suggests that health in Spain has continued to improve during the first four years of the current economic recession, so it seems this bias would be reduced [171,355].

Chapter 5
Conclusions

- Multimorbidity is present in a large proportion of the Spanish older population, especially in those aged over 50. The prevalence of multimorbidity reaches up to over half and two thirds of men and women over 65 years respectively. Chronic conditions tend to appear in certain multimorbidity patterns: “cardio-respiratory” (angina, asthma, COPD), “mental-arthritis” (arthritis, anxiety, depression), “aggregate pattern” (angina, cataract, hypertension, edentulism, diabetes, arthritis, stroke).

- The number of chronic conditions is strongly associated with a diagnosis of depression and anxiety.

- With regard to the analysis of the impact of individual physical diseases on mental health, a higher risk of depression is present in people with asthma, angina, COPD and arthritis, whereas only angina is associated with anxiety.

- Visual impairment is common in the Spanish older population. Stroke, arthritis and diabetes are associated individually with worse distance visual acuity, while stroke is associated with worse near visual acuity. The number of physical conditions is strongly associated with worse distance and near visual acuity.

- Subjective distance visual acuity problems are related to a higher risk of depression, while no measure of visual acuity is associated with changes in the prevalence of anxiety. All measures of visual impairment (distance/near and objective/subjective) are related to impaired cognitive functioning.

- All chronic conditions assessed (angina, anxiety, arthritis, asthma, cataract, COPD, depression, diabetes, edentulism, stroke), except for hypertension, impact negatively on disability and quality of life in the Spanish older population. Stroke and mental disorders (depression, anxiety) are the conditions that most strongly impact on these outcomes. Conditions with fewer symptoms (diabetes, edentulism, cataract) tend to have a lower impact on health outcomes compared with those with more symptoms (angina, COPD, arthritis). The number of chronic conditions impacts greatly both on quality of life and disability.

- Women have moderately poorer results in quality of life and disability than men. Individually, some conditions appear only in men or in women. The effect of the number of chronic conditions is important in both sexes.

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Annex I

Visual care characteristics in the Spanish general adult population

Visual care characteristics in the Spanish general adult population.

		TOTAL	18-49 years		50-64 years		> 65 years		p (age)	p (sex)
			Men	Women	Men	Women	Men	Women		
Last visual check									<0.001	0.007
	Last year	30.4 (28.3-32.7)	31.4 (27.1-36.1)	24.9 (21.4-28.8)	29.8 (26.9-32.8)	31.9 (29.3-34.6)	35.5 (32.0-39.1)	37.6 (33.4-41.9)		
	1-5 years	53.3 (51.0-55.5)	47.1 (42.6-51.6)	58.1 (54.0-62.0)	59.1 (55.7-62.5)	58.4 (55.2-61.5)	50.1 (45.2-55.0)	51.5 (47.9-55.1)		
	5+ years	9.0 (7.7-10.4)	9.6 (7.2-12.8)	9.1 (6.9-12.0)	7.4 (5.7-9.5)	7.3 (5.5-9.6)	10.4 (7.5-14.4)	8.4 (6.2-11.1)		
	Never	7.3 (6.0-8.9)	11.9 (8.8-15.9)	7.9 (5.8-10.8)	3.7 (2.5-5.6)	2.5 (1.6-3.8)	4.0 (2.8-5.6)	2.6 (1.6-4.3)		
Distance glasses									<0.001	0.02
	No	58.9 (57.0-60.7)	68.8 (64.4-72.8)	67.3 (63.4-71.0)	53.7 (50.3-57.1)	45.4 (41.9-48.9)	53.7 (50.3-57.1)	37.7 (34.6-41.0)		
	Yes	41.1 (39.3-43.0)	31.2 (27.2-35.6)	32.7 (29.0-36.6)	46.3 (42.9-49.7)	54.6 (51.1-58.1)	46.3 (42.9-49.7)	62.3 (59.0-65.4)		
Near glasses									<0.001	<0.001
	No	48.5 (46.5-50.6)	74.8 (70.8-78.4)	63.7 (58.9-68.2)	19.7 (17.2-22.5)	13.4 (10.6-16.7)	17.2 (14.2-20.6)	13.3 (11.0-16.0)		
	Yes	51.5 (49.4-53.5)	25.2 (21.6-29.2)	36.3 (31.8-41.1)	80.3 (77.5-82.8)	86.6 (83.3-89.4)	82.8 (79.4-85.8)	86.7 (84.0-89.0)		

Information on visual care history and use of glasses was obtained through self-reported data from the respondents. Weighted proportion and 95% confidence intervals are shown; *p*(age) refers to statistical differences in the three age groups; *p*(sex) refers to differences in gender, regardless the age group; subjective visual acuity is assessed as vision problems mentioned by the patient.

Annex II

Publications not included in this thesis

- Tyrovolas S, Koyanagi A, Garin N, Olaya B, Ayuso-Mateos M, Miret M, Chatterji S, Tobias-Adamczyk B, Koskinen S, Leonardi M, Haro JM. **Determinants of the components of arterial pressure among older adults–the role of anthropometric and clinical factors: a multi-continent study.** *Atherosclerosis.* 2014 Dec 12. 238(2):240-249.

- Koyanagi A, Garin N, Olaya B, Ayuso-Mateos JL, Chatterji S, Leonardi M, Koskinen S, Tobiasz-Adamczyk B, Haro JM**. Chronic Conditions and Sleep Problems among Adults Aged 50 years or over in Nine Countries: A Multi-Country Study.** *PLoS One.* 2014 Dec 5;9(12):e114742. doi: 10.1371/journal.pone.0114742. eCollection 2014.

- Haro J, Tyrovolas S, Garin N, Diaz-Torne C, Carmona L, Riera L, Perez-Ruiz F, Murray C. **The burden of disease in Spain: results from the global burden of disease study 2010.** *BMC Med.* 2014 Dec 5;12(1):236-39. doi:10.1186/s12916-014-0236-9

- Lara E, Garin N, Ferrari AJ, Tyrovolas S, Olaya B, Sànchez-Riera L, Whiteford HA, Haro JM. **The Spanish Burden of Disease 2010: Neurological, mental and substance use disorders.** *Rev Psiquiatr Salud Ment.* 2014 Nov 26. pii: S1888-9891(14)00105-0. doi: 10.1016/j.rpsm.2014.09.001

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